C5a Receptor Antagonists

The present invention is related to antagonists of the C5a receptor and the use thereof.

Prior Art

Besides the adaptive immune system another - developmental much older - system for the defence against infection exists. This system is called complement system and consists of more than 30 soluble and membrane bound proteins. The complement system can be activated without or together with the adaptive immune system to eliminate, e.g., pathogenic bacteria. An uncontrolled activation or inadequate regulation of the complement system is related to a number of inflammatory diseases like septic shock, reperfusion injury, rheumatoid arthritis, transplant rejection, acute respiratory distress syndrome (ARDS), systemic lupus erythematosis (SLE), and glomerulonephritis. Numerous overviews over the relation between the complement system and diseases are published (e.g. Kirschfink 1997 Immunopharmacology 38: 51-62; Markides 1998 Pharmacological Reviews 50: 59-87, Walport 2001 The New England Journal of Medicine 344: 1140-1144, Walport 2001 The New England Journal of Medicine 344: 1058-66).

Activation of the complement system takes place via three different pathways. They are called classical, alternative, and mannose-binding lectin (MBL) way. All pathways proceed via the sequential processing and thus activation of pro-forms of proteases. As each activated protease can cleave and therefore activate the next pro-form, an amplification of the initial reaction is obtained. This is similar to the clotting cascade. An overview over the complement system is given by Sim and Laich (2000 Biochemical Society Transactions 28: 545-550).

Some of the most important proteins that are generated upon complement activation are C3a, C3b, C5a, and C5b. These proteins will be discussed in detail.

C3b is an essential part of a central protease of the complement cascade, the C5 convertase. C3b is part of the C5 convertase from both, the classical and alternative pathway of complement activation. The MLB pathway is proceeding via the convertases of the classical pathway, too. The C5 convertase is responsible for the progress of the complement cascade and catalyses the cleavage of C5. Additionally, C3b is covalently attached to the surface of, e. g., bacteria which

are thus more prone to phagocytosis by macrophages. Similar processes are described for immune complex clearance.

C3a is the smaller fragment that is produced in addition to C3b upon cleavage of C3. C3a is a comparatively weak chemokine and belongs to the anaphylatoxins.

C5b is formed by cleavage of C5. This cleavage product is the starting point for the formation of the membrane attack complex (MAC). The MAC forms a pore which perforates both plasma membranes of bacteria and endogenous cells. Due to the pore formation the perforated cells can be lysed.

C5a is the 74 amino acid N-terminal cleavage product of the α-chain of plasma protein C5 and is released by the activity of the C5 convertase. C5a is bound by its receptor which is referred to as C5a receptor C5aR1 or CD88, with high affinity and triggers a number of pro-inflammatory effects. It is one of the most potent chemokines and belongs as C3a to the anaphylatoxins. The C5aR can be found on many cells. This receptor is particularly found on neutrophils, macrophages, smooth muscle cells, and endothelial cells.

C5a release is thought to be directly or indirectly responsible for many diseases. Examples are sepsis (Huber-Lang et al. 2001 Faseb Journal 15: 568-570), multiple sclerosis (Mullerladner et al. 1996 Journal of Neurological Science 144: 135-141), reperfusion injury (Riley et al. 2000 Journal of Thoriacic and Cardiovascular Surgery 120: 350-358), psoriasis (Bergh et al. 1993 Archives of Dermatological Research 285: 131-134), rheumatoid arthritis (Woodruff et al. 2002 Arthritis and Rheumattism 46: 2476-85) und immune complex associated diseases in general (Heller et al. 1999 Journal of Immunology 163: 985-994). An overview over C5a related diseases is found in Köhl (2001 Molecular Immunology 38: 51-62).

Although it is obvious that C5a is responsible for many of the symptoms of inflammatory diseases, until today no drug directly aiming at the interaction between the receptor and its ligand was approved. The C5aR is a particularly interesting target. This is especially the case due to the finding that mice lacking the receptor do not show an unusual phenotype (Hopken et al. 1996 Nature 383: 86-89). This means that the complement cascade with its useful functions for defence against pathogens (MAC formation) and immune complex clearance can still proceed in an unhindered manner even when the receptor is totally inactivated.

The development of a specific C5a receptor antagonist also referred to herein as C5aR antagonist, was part of past programs. Among others, small molecules have been looked for. Examples for such molecules are L-156602 (Merck), RPR120033 (Rhone-Poulenc), W-54011 (Mitsubishi Pharma), and NGD 2000-1 (Neurogen). All currently known inhibitors with a molecular weight of <500 g/mol have at least one of the following drawbacks: low specificity, agonistic properties, too low affinity, poor solubility, inadequate metabolic stability, or inhibition of P450 enzymes.

Another way for the development of C5aR inhibitors is based on the use of recombinant proteins. Examples for such protein based antagonists are CGS 32359 (Ciba-Geigy, Pellas et al. 1998 Journal of Immunology 160: 5616-5621), ΔpIII-A8 (Heller et al. 1999 Journal of Immunology 163: 985-994) and antibodies, which can be of recombinant or non-recombinant origin (Huber-Lang et al. 2001 Faseb Journal 15: 568-570). These C5aR antagonists are proteins and therefore expensive in production. They have comparatively high affinities and specificities but have the drawback of pronounced immunogenicity. In addition, proteins can be effectively administered only by costly procedure such as, e. g., injection.

The C-terminal sequence information of C5a was used for the development of peptidic C5aR antagonists. Peptides as therapeutically useable antagonists of the C5aR are advantageous over protein therapeutics because of lower production costs, reduced immunogenicity, and high plasma stability. In addition they are more specific than most of the currently known small molecules. Many peptidic antagonists are described in the literature. A common feature of nearly all C5aR antagonists is their origin in the C-terminus of C5a. Examples for these peptidic C5aR antagonists or partial agonists are found in the following patents and patent applications: US 4,692,511, US 5,663,148, WO 90/09162, WO 92/11858, WO 92/12168, WO 92/21361, WO 94/07518, WO 94/07815, WO 95/25957, WO 96/06629, WO 99/00406 und WO 99/13899, WO 03/033528.

Nearly all of the described peptides which bind to the C5aR, carry the positively charged amino acid arginine at the C-terminus. Sequences of these peptides were disclosed both in scientific literature (Finch et al. 1999 Journal of Medicinical Chemistry 42: 1965-1974; Wong et al. 1999 IDrugs 2: 686-693; Psczkowski et al. 1999 Pharmacology 128: 1461-1466) and in the above recited patents and patent applications. WO 90/09162 discloses 38 peptidic inhibitors with their

IC_{50} values. 37 thereof have a C-terminal arginine and one peptide varies a C-terminal tyrosine. The substitution of the C-terminal arginine resulted, in this example, in a significant loss in affinity. The lowest IC_{50} value of the compounds of these patent applications is 0.011 μM. In contrast thereto, a tyrosine at the C-terminus results in an IC_{50} value of 0.17 μM. In the functional assay systems used in the instant application, this compound has an IC_{50} value of 1.3 μM.

WO92/12168 discloses 20 peptides by means of their IC_{50} values (binding to C5aR). 19 thereof have a terminal arginine which may be present in either the D-form or the L-form. One peptide bears a phenylbutanoyl residue at the C-terminus. This peptide shows an IC_{50} value of only 2.6 μM.

Among the 22 peptides of WO 94/07518 for which IC_{50} values have been presented, all peptides have a C-terminal arginine.

The IC_{50} values indicated in the recited applications are derived from measurements with isolated membranes from polymorphonuclear neutrophilic granulocytes (PMN membranes) because at the time when these experiments were performed, C5a overexpressing cells could not be generated. Results from these measurements do not reflect the affinity of the compounds to whole cells. The compounds have usually a reduced affinity to receptors on whole cells (Kawai et al. 1991 Journal of Medicinal Chemistry 34: 2068-71; Rollins et al. 1988 Journal of Biological Chemistry 263: 520-526). It is more meaningful to measure the biological activity rather than the binding of the antagonist to the receptor. Often such functional assays are used for G protein coupled receptors.

The examples presented in international patent applications WO 95/25957 und WO 96/06629 for which IC_{50} values are known, are without any exception peptides containing a C-terminal arginine.

In WO 99/00406 a number of cyclic and linear peptidic inhibitors are described. Their common feature is the C-terminal arginine. A model of the pharmacophore which is outlined in WO 99/00406 is directly pointing towards the required positive charge which can be realised by arginine.

This is also reflected in the sequence of C5a which also beras an arginine residue at the C-terminus. The agonistic potency is reduced by a factor 10 to 100, when this arginine is cleaved off by carboxypeptidases (C5a-desArg).

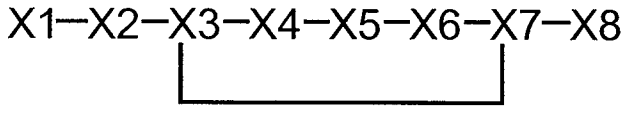
In WO 03/033528 single substitutions of various amino acids in the molecule Ac-Phe[Orn-Pro-cha-Trp-Arg] are reported. A decrease of the affinity to the C5aR and a decrease in antagonistic potency is shown for the substitution of the Arg with homoarginine, citrulline or lysine. IC_{50} values (binding) are 6 µM, 24 µM and 1,4 µM, respectively, for the three described arginine substitutions (the starting material bears a C-terminal arginine and has an IC_{50} of 0,3 µM as indicated in WO 99/00406.). This underlines the importance of the C-terminal arginine.

In a review of Morikis and Lambris (2002 Biochemical Society Transactions 30: 1026-1036) the importance of the arginine for the affinity of agonists and antagonists to the C5a receptor is stressed.

It is apparent that the prior art requires a C-terminal localized positive charge for peptidic and peptidomimetic C5a ligands with noteworthy inhibitory activity (IC_{50} < 200 nM). This charge is realized usually by arginine.

The problem underlying the present application is the provision of C5aR antagonists. Another problem underlying the present invention is the provision of drugs, that can be used for the treatment of diseases, in which the C5a receptor is involved in a causal manner.

In a first aspect of the invention the problem is solved by a compound, preferably a C5a receptor antagonist, with the following structure:



(I)

, whereby

X1 is a radical having a mass of about 1-300 and whereby X1 is preferably chosen from the group including R5-, R5-CO-, R5-N(R6)-CO-, R5-O-CO-, R5-SO_2-, R5-N(R6)-SO_2-, R5-N(R6)-, R5-N(R6)-CS-, R5-N(R6)-C(NH)-, R5-CS-, R5-P(O)OH-, R5-B(OH)-, R5-CH=N-O-CH_2-CO-, in which R5 and R6 individually and independently are chosen from the group comprising H, F, hydroxy, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, arylalkyl, substituted arylalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, acyl, substituted acyl, alkoxy, alkoxyalkyl, substituted alkoxyalkyl, aryloxyalkyl and substituted aryloxyalkyl,

X2 is a radical that mimics the biologic binding characteristics of a phenylalanine unit,

X3 and X4 individually and independently are a spacer, whereby the spacer is preferably selected from the group comprising amino acids, amino acid analogs and amino acid derivates,

X5 is a radical that mimics the biologic binding characteristics of a cyclohexylalanine unit,

X6 is a radical that mimics the biologic binding characteristics of a tryptophane unit,

X7 is a radical that mimics the biologic binding characteristics of a norleucine or phenylalanine unit,

X8 is a radical, whereby the radical is optionally contained in structure I and if it is contained, it is selected from the group comprising H, NH_2, OH, NH-OH, amino, substituted amino, alkoxy, substituted alkoxy, hydrazine, substituted hydrazine, aminooxy, substituted aminooxy, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, heteroaryl, substituted heteroaryl, Arylalkyl, substituted Arylalkyl, aryl, substituted aryl, amino acid, amino acid derivative and amino acid analogues.

a chemical bond is formed between X3 and X7, and

the lines – in formula (I) indicate chemical bonds, whereby the chemical bond is preferably selected from the group comprising covalent bonds, ionic bonds and coordinative bonds,

whereby preferably the bond is a chemical bond and more preferably the chemical bond is a bond selected from the group comprising amide bonds, disulfide bonds, ether bonds, thioether bonds, oxime bonds and aminotriazine bonds.

In an embodiment X3 and X7 are individually an amino acid, amino acid analog or amino acid derivative, whereby the chemical bond between X3 and X7 is formed under participation of moieties of X3 and X7, and the moieties for X3 and X7 are individually and independently selected from the group comprising the C terminus, the N terminus and the respective side chain of the amino acid.

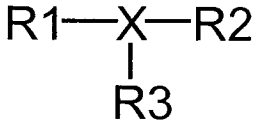
In a further embodiment X1 is a radical with a mass of about 1-300, whereby the radical is preferably selected from the group comprising R5, R5-CO-, R5-N(R6)-CO-, R5-O-CO-, R5-SO_2-, R5-N(R6)-C(NH)-, whereby R5 and R6 are individually and independently selected from the group comprising H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl and substituted aryl;

X2 and X6 are individually and independently an aromatic amino acid, a derivative or an analogon thereof;

X5 and X7 are individually and independently a hydrophobic amino acid, a derivative or an analogon thereof.

In a specific embodiment X1 is selected from the group comprising H, actetyl, propanoyl, butanoyl, benzoyl, fluoromethylcarbonyl, difluoromethylcarbonyl, phenyl, oxycarbonyl, methyl-oxycarbonyl, phenyl-aminocarbonyl, methyl-aminocarbonyl, phenyl-sulfonyl and methyl-sulfonyl.

In an embodiment X2, X5, X6 and X7 individually and independently have the following structure:



(III),

wherein

X is C(R4) or N,

R1 is optionally present and if present then R1 is a radical, that is selected from the group comprising >N-R1B, >C(R1B)(R1C) and >O, whereby R1B and R1C are individually and independently selected from the group comprising H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, arylalkyl, substituted arylalkyl, cycloalkylalkyl and substituted cycloalkylalkyl;

R2 is optionally present and if R2 is present then R2 is a radical that is selected from the group comprising C=O, C=S, SO_2, S=O, C=NH, C=N-CN, PO(OH), B(OH), CH_2, CH_2CO, CHF and CF_2;

R4 is a radical, whereby the radical is selected from the group comprising H, F, CH_3, CF_3, alkyl and substituted alkyl;

the binding of structure (III) to the moieties X1 and X3, X4 and X6, X5 and X7, and X6 and X8 is preferably carried out via R1 and R2;

for X2 and for X6 individually and independently R3 is a radical, in which the radical comprises an aromatic group and is selected from the group comprising aryl, substituted aryl, heteroaryl, substituted heteroaryl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, alkyloxy-alkyl, substituted alkyloxy-alkyl, alkyloxy-cycloalkyl, substituted alkyloxy-cycloalkyl, alkyloxy-heterocyclyl, substituted alkyloxy-heterocyclyl, alkyloxy-aryl, substituted alkyloxy-aryl, alkyloxy-heteroaryl, substituted alkyloxy-heteroaryl, alkylthio-alkyl, substituted alkylthio-alkyl, alkylthio-cycloalkyl and substituted alkylthio-cycloalkyl; and

for X5 and for X7 individually and independently R3 is a radical, whereby the radical comprises an aliphatic or aromatic group and preferably is seletected from the group comprising alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, arylalkyl, substituted arylalkyl,

heteroarylalkyl, substituted heteroarylalkyl, cycloalkylalkyl, substituted cycloalkylalkyl, heterocyclylalkyl, substituted heterocyclylalkyl, alkyloxy-alkyl, substituted alkyloxy-alkyl, alkyloxy-cycloalkyl, substituted alkyloxy-cycloalkyl, alkyloxy-heterocyclyl, substituted alkyloxy-heterocyclyl, alkyloxy-aryl, substituted alkyloxy-aryl, alkyloxy-heteroaryl, substituted alkyloxy-heteroaryl, alkylthio-alkyl, substituted alkylthio-alkyl, alkylthio-cycloalkyl and substituted alkylthio-cycloalkyl.

In a particular embodiment a ring is formed under participation of R3 and R4.

In a further embodiment, for X2 and for X6 individually and independently R3 is selected from the group comprising phenyl, substituted phenyl, benzyl, substituted benzyl, 1,1-diphenylmethyl, substituted 1,1-diphenylmethyl, naphthylmethyl, substituted naphthylmethyl, thienylmethyl, substituted thienylmethyl, benzothienylmethyl, substituted benzothienylmethyl, imidazolylmethyl, substituted imidazolylmethyl, indolylmethyl and substituted indolylmethyl.

In a still futher embodiment, for X5 and for X7 individually and independently R3 is selected from the group comprising C3-C5-alkyl, substituted C3-C5-alkyl, C5-C7-cycloalkyl, substituted C5-C7-cycloalkyl, C5-C7-cycloalkylmethyl, substituted C5-C7-cycloalkylmethyl, cycloalkylethyl, substituted cycloalkylethyl, benzyl, substituted benzyl, phenylethyl, naphthylmethyl, thienylmethyl, propenyl, propinyl, methylthioethyl, imidazolylmethyl, substituted imidazolylmethyl, indolylmethyl and substituted indolylmethyl.

As used herein, C3-C5-alkyl refers to a residue consisting of 3, 4 or 5 C-atoms and substituted C3-C% refers to a residue consisting of 3, 4 or 5 C-atoms, whereby any atom may carry one or more substitutents. *n*-propyl, *n*-butyl, *n*-pentyl, *i*-pentyl, *i*-propyl, *i*-butyl and *i*-pentyl are particularly preferred C3-C5-alkyl residues. It is within the present invention that these particularly preferred C3-C5-alkyl residues carry one or more substitutents.

As used herein, C5-C7-cycloalkyl refers to a cyclic residue consisting of 5, 6 or 7 C-atoms, and substituted C5-C7-cycloalkyl refers to a cyclic residue consisting of 5, 6 or 7 C-atoms, whereby each of the atoms may carry a substituent. Cycloheptyl, cyclohexyl and cyclopentyl are particularly preferred C5-C7-cycloalkyl residues, whereby it is within the present invention that these particularly preferred C5-C7-cycloalkyl residues carry one or more substitutents.

As used hierein, C5-C7-cycloalkylmethyl refers to a cycloalkyl residue bound to the remainder of the moleculr *via* a methylene residue.

As used herein, cycloalkylmethyl refers to a cycloalkyl residue bound to the remainder of the molecule *via* a methylene residue.

In an embodiment X2 of the compound according to the invention, it is contemplated that X2 is a derivative of an amino acid that is selected from the group comprising phenylalanine, 2-fluoro-phenylalanine, 3-fluoro-phenylalanine, 4-fluoro-phenylalanine, 2-chlorophenylalanines, 3-chlorophenylalanines, 4-chlorophenylalanines, 1-naphtylalanines, 2-thienylalanines, 3-thienylalanines, 3,3-diphenylalanines, tyrosine, tryptophane, histidine and each respective derivatives thereof;

or X2 and X1 taken together are $PhCH_2CH_2CO$- or $PhCH_2$-;

X6 is a derivative of an amino acid, that is selected from the group comprising tryptophane, phenylalanine, tyrosine, histidine, 1-naphtylalanine, benzothienylalanine, 2-aminoindan-2-carboxylic acid, 2-thienylalanine, 3-thienylalanine, 2-fluoro-phenylalanine, 3-fluoro-phenylalanine, 4-fluoro-phenylalanine, 2-chlorophenylalanines, 3-chlorophenylalanines, 4-chlorophenylalanines and respective derivatives thereof;

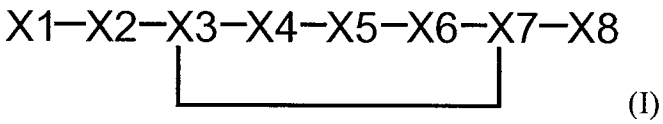
X5 is a derivative of an amino acid that is seletected from the group comprising D-cyclohexylalanine, D-cyclohexylglycine, D-homo-cyclohexylalanine, octahydroindol-2-carboxylic acid, 2-methyl-D-phenylalanine and respective derivatives thereof; and

X7 is a derivative of an amino acid that is seletected from the group comprising norvaline, norleucine, homo-leucine, leucine, isoleucine, Valine, cysteine, cysteine(Me), cysteine(Et), cysteine(Pr), methionine, allylglycine, propargylglycine, cyclohexylglycine, cyclohexylalanine, phenylalanine, tyrosine, tryptophane, histidine, 1-naphtylalanine, 2-thienylalanine, 3-thienylalanine and respective derivatives thereof.

In a further embodiment X1 and/or X4 comprise one or more groups that improve water solubility, whereby the water solubility improving group is seletected from the group comprising

hydroxy, keto, carboxamido, ether, urea, carbamate, amino, substituted amino, Guanidino, pyridyl and carboxyl.

In a second aspect of the invention the problem is solved by a compound, preferably a C5a receptor antagonist, having the following structure:



(I)

, whereby X1-X3 and X5-X8 are defined as defined in the context of the compound in accordance with the first aspect of the present invention and whereby

X4 is a cyclic or a non-cyclic amino acid, whereby the cyclic amino acid is seletected from the group comprising proline, pipecolinic acid, azetidine-2-carboxylic acid, tetrahydroisochinoline-3-carboxylic acid, tetrahydroisochinoline-1-carboxylic acid, octahydroindole-2-carboxylic acid, 1-aza-bicyclo-[3.3.0]-octane-2-carboxylic acid, 4-phenyl-pyrrolidine-2-carboxylic acid, cis-Hyp and trans-Hyp, and whereby the non-cyclic amino acid is selected from the group comprising Ser, Gln, Asn, Cys($O_2CH_2CH_2CONH_2$), Arg, Hyp($COCH_2OCH_2CH_2OCH_2CH_2OCH_3$), Hyp($CONH\text{-}CH_2CH(OH)\text{-}CH_2OH$) and respective derivatives thereof and respective analogs thereof; and

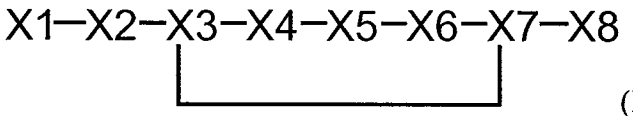
the lines – in formula (I) indicate chemical bonds, whereby the chemical bond is preferably selected from the group comprising covalent bonds, ionic bonds and coordinative bonds, whereby preferably the bond is a chemical bond and more preferably the chemical bond is a bond selected from the group comprising amide bonds, disulfide bonds, ether bonds, thioether bonds, oxime bonds and aminotriazine bonds.

In an embodiment, it is contemplated that derivatives and/or analogues are such that individual or several hydrogen atoms of the indicated aimno acids may be substituted.

In an embodiment the amino acids are preferably selected from the group comprising proline, pipecolinic acid, azetidine-2-carboxylic acid, tetrahydroisochinoline-3-carboxylic acid, tetrahydroisochinoline-1-carboxylic acid, octahydroindole-2-carboxylic acid, 1-aza-bicyclo-[3.3.0]-octane-2-carboxylic acid, 4-phenyl-pyrrolidine-2-carboxylic acid, Hyp, Ser, Gln, Asn, Cys($O_2CH_2CH_2CONH_2$) and Arg.

The compounds referred to by the above abbreviations are, again, defined herein in Table 3.

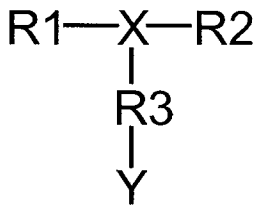
In a third aspect the problem is solved according to the invention by a compound, preferably a C5 receptor antagonist of the structure



(I),

whereby X1-X2 and X4-X8 are defined as in the context of the compound according to the first and second aspect of the invention, whereby

X3 has the following structure



(IV),

wherein

X is C(R4) or N,

R1 is optionally present and if R1 is present then R1 is a radical which is selected from the group comprising >N-R1B, >C(R1B)(R1C) and >O, whereby R1B and R1C are individually and independently selected from the group comprising H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, arylakyl, substituted arylalkyl, cycloalkylalkyl and substituted cycloalkylalkyl;

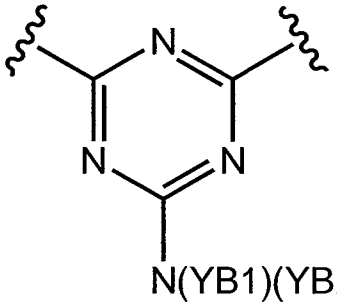
R2 is optionally present and if R2 is present then R2 is a radical that is selected from the group comprising C=O, C=S, SO_2, PO(OH), B(OH), CH_2, CH_2CO, CHF and CF_2;

R4 is a radical, whereby the radical is selected from the group comprising H, F, CF_3, alkyl and substituted alkyl;

the binding of structure (IV) to the moieties X2 and X4 preferably takes place via R1 and R2;

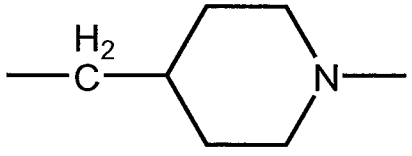
R3 is a radical, whereby the radical is selected from the group comprising H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkylalkyl, substituted cycloalkylalkyl, heterocyclylalkyl, substituted heterocyclylalkyl, arylalkyl, substituted arylalkyl, heteroarylalkyl and substituted heteroarylalkyl.

Y is optionally present and if Y is present then Y is a radical that is selected from the group comprising – N(YB)-, -O-, -S-, -S-S-, -CO-, -C=N-O-, -CO-N(YB)- and



, whereby YB, YB1 and YB2 are individually and independently selected from the group comprising H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, arylakyl, substituted arylalkyl, cycloalkylalkyl and substituted cycloalkylalkyl.

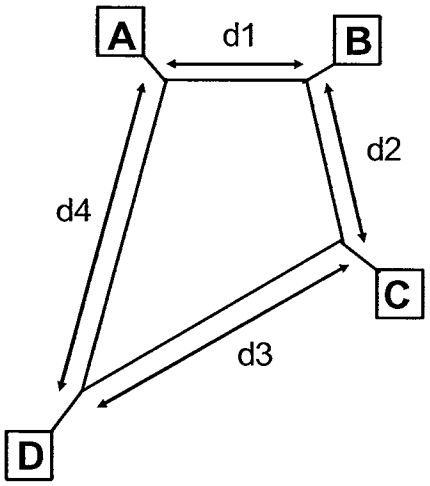
In an embodiment R3 is a radical selected from the group comprising methyl, ethyl, propyl, butyl, benzyl and



;

Y is optionally present and if Y is present then Y is a radical selected from the group comprising –N(YB)-, -O-, -S- and -S-S-.

In a fourth aspect of the invention the problem is solved by a compound, preferably a C5a receptor antagonist, whereby the compound has the following structure:



whereby d1, d2, d3 and d4 represent the distances of A, B, C and D in at least one energetically accessible conformer of the compound and have the following values:

d1 = 5.1 ± 1.0 Å

d2 = 11.5 ± 1.0 Å

d3 = 10.0 ± 1.5 Å

d4 = 6.9 ± 1.5 Å

A and C are individually and independently a hydrophobic radical, whereby the hydrophobic radical is selected from the group comprising alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

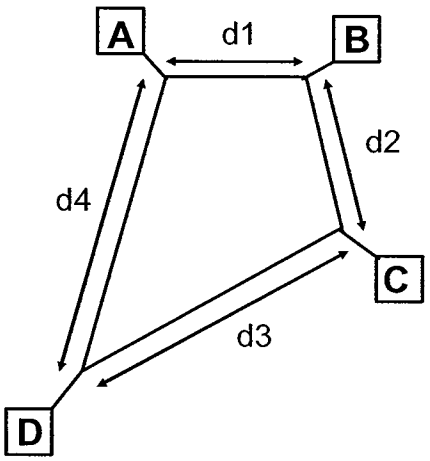
B and D are individually and independently an aromatic or a heteroaromatic radical, whereby preferably the aromatic radical is aryl, and preferably the heteroaromatic radical is heteroaryl.

In an embodiment A and C are individually and independently selected from the group comprising C3-C6-alkyl, C5-C7-cycloalkyl, methylthioethyl, indolyl, phenyl, naphtyl, thienyl, propenyl, propinyl, hydroxyphenyl, indolyl and imidazolyl;

B is selected from the group comprising phenyl, naphthyl, thienyl, benzothienyl, hydroxyphenyl, indolyl, and imidazolyl; and

D is selected from the group comprising phenyl, naphthyl, thienyl, thiazolyl, furanyl, hydroxyphenyl, indolyl and imidazolyl.

In a fifth aspect of the invention the problem is solved by a compound, preferably a C5a receptor antagonist, having the following structure:



, whereby

A, B, C and D represent the C-alpha atoms in amino acids, amino acid analogs or amino acid derivatives,

d1, d2, d3 and d4 represent the distances of A, B, C and D in at least one energetically accessible conformer of the compound and have the following values:

d1 = 3,9 ± 0,5 Å

d2 = 3,9 ± 0,5 Å

d3 = 9,0 ± 1,5 Å

d4 = 9,0 ± 1,5 Å;

A and C individually and independently have a hydrophobic amino acid side chain that comprises an alkyl-, cycloalkyl, cycloalkylalkyl, heterocyclyl, aryl or heteroaryl group,

B and D individually and independently have an aromatic or heteroaromatic amino acid side chain that comprises an aryl or heteroaryl group.

In an embodiment the A is seletected from the group comprising C3-C6-alkyl, methylthioethyl, propenyl, propinyl, R5, methyl-R5 and ethyl-R5, whereby R5 is a radical that is selected from the group comprising C5-C7-cycloalkyl, phenyl, substituted phenyl, hydroxyphenyl, indolyl, imidazolyl, naphtyl and thienyl;

B is selected from the group comprising R5, methyl-R5 and ethyl-R5, whereby R5 is selected from the group comprising phenyl, substituted phenyl, naphtyl, thienyl, benzothienyl, hydroxyphenyl, indolyl and imidazolyl;

C is selected from the group comprising C3-C6-alkyl, R5, methyl-R5 and ethyl-R5, whereby R5 is a radical that is selected from the group comprising C5-C7-cycloalkyl, phenyl, 1-methyl-phenyl, 2-methyl-phenyl, 3-methyl-phenyl and S-tBu; and

D is selected from the group comprising R5, methyl-R5 and ethyl-R5, whereby R5 is a radical, that is selected from the group comprising phenyl, naphthyl, thienyl, thiazolyl, furanyl, hydroxyphenyl, indolyl and imidazolyl.

In a sixth aspect of the invention the problem is solved by a compound, preferably a C5a receptor antagonist, having the following structure:

X1–X2–X3–X4–X5–X6–X7–X8 (II)

, whereby

X1 is a radical having a mass of about 1-300 and whereby X1 is preferably selected from the group comprising R5-, R5-CO-, R5-N(R6)-CO-, R5-O-CO-, R5-SO_2-, R5-N(R6)-SO_2-, R5-N(R6)-, R5-N(R6)-CS-, R5-N(R6)-C(NH)-, R5-CS-, R5-P(O)OH-, R5-B(OH)-, R5-CH=N-O-CH_2-CO-, whereby R5 and R6 are individually and independently selected from the group comprising H, F, hydroxy, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, arylalkyl, substituted arylalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, acyl, substituted acyl, alkoxy, alkoxyalkyl, substituted alkoxyalkyl, aryloxyalkyl and substituted aryloxyalkyl,

X2 is a radical that mimics the biological binding characteristics of a phenylalanine unit,

X3 and X4 are individually and independently a spacer, whereby the spacer is preferably selected from the group comprising amino acids, amino acid analogs and amino acid derivates,

X5 is a radical that mimics the biological binding characteristics of a cyclohexylalanine unit,

X6 is a radical that mimics the biological binding characteristics of a tryptophane unit,

X7 is a radical that mimics the biological binding characteristics of a norleucine or phenylalanine unit,

X8 is a radical, whereby the radical is optionally present in structure I, and if it is present, it is selected from the group comprising H, NH_2, OH, NH-OH, amino, substituted amino, alkoxy, substituted alkoxy, hydrazino, substituted hydrazino, aminooxy, substituted aminooxy, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, heteroaryl, substituted heteroaryl, arylalkyl, substituted arylalkyl, aryl, substituted aryl, amino acid, amino acid derivative and amino acid analogon;

the connecting lines – in formula (II) represent chemical bonds, whereby the chemical bond is selected from the group comprising covalent bonds, ionic bonds and coordinative bonds, whereby preferably the bond is a chemical bond and more preferably the chemical bond is a bond selected from the group comprising amide bonds, disulfide bonds, ether bonds, thioether bonds, oxime bonds and aminotriazine bonds.

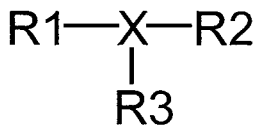
In an embodiment X1 is a radical having a mass of about 1-300, whereby the radical is preferably selected from the group comprising R5, R5-CO-, R5-N(R6)-CO-, R5-O-CO-, R5-SO_2-, R5-N(R6)-C(NH)-, whereby preferably R5 and R6 are individually and independently selected from the group comprising H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl and substituted aryl;

X2 and X6 are individually and independently an aromatic amino acid, a derivative or an analogon thereof,

X5 and X7 are individually and independently a hydrophobic amino acid, a derivative or an analogon thereof.

In a preferred embodiment, X1 is selected from the group comprising H, acetly, propanoyl, butanoyl, benzoyl, frluormethylcarbonyl, difluoromethylcarbonyl, phenyl, oxycarbonyl, methoxycarbonyl, phenylaminocarbonyl, methylaminocarbonyl, phenylsulfonyl and methylsulfonyl.

In an embodiment X2, X5, X6 and X7 have individually and independently the following structure:



(III),

whereby

X is C(R4) or N,

R1 is a radical that is selected from the group comprising >N-R1B, >C(R1B)(R1C) and >O, whereby R1B and R1C are individually and independently selected from the group comprising H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, arylalkyl, substituted arylalkyl, cycloalkylalkyl and substituted cycloalkylalkyl;

R2 is optionally present and if R2 is present, it is a radical selected from the group comprising C=O, C=S, SO_2, S=O, C=NH, C=N-CN, PO(OH), B(OH), CH_2, CH_2CO, CHF and CF_2;

R4 is a radical, whereby the radical is selected from the group comprising H, F, CH_3, CF_3, alkyl and substituted alkyl;

and the binding of structure (III) to the moieties X1 and X3, X4 and X6, X5 and X7, and X6 and X8 preferably takes place via R1 and R2;

for X2 and for X6 individually and independently R3 is a radical, whereby the radical comprises an aromatic group and is selected from the group comprising aryl, substituted aryl, heteroaryl, substituted heteroaryl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, alkyloxy-alkyl, substituted alkyloxy-alkyl, alkyloxy-cycloalkyl, substituted alkyloxy-cycloalkyl, alkyloxy-heterocyclyl, substituted alkyloxy-heterocyclyl, alkyloxy-aryl, substituted alkyloxy-aryl, alkyloxy-heteroaryl, substituted alkyloxy-heteroaryl, alkylthio-alkyl, substituted alkylthio-alkyl, alkylthio-cycloalkyl and substituted alkylthio-cycloalkyl; and

for X5 and for X7 individually and independently R3 is a radical, whereby the radical comprises an aliphatic or aromatic group and preferably is selected from the group comprising alkyl,

substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, cycloalkylalkyl, substituted cycloalkylalkyl, heterocyclylalkyl, substituted heterocyclylalkyl, alkyloxy-alkyl, substituted alkyloxy-alkyl, alkyloxy-cycloalkyl, substituted alkyloxy-cycloalkyl, alkyloxy-heterocyclyl, substituted alkyloxy-heterocyclyl, alkyloxy-aryl, substituted alkyloxy-aryl, alkyloxy-heteroaryl, substituted alkyloxy-heteroaryl, alkylthio-alkyl, substituted alkylthio-alkyl, alkylthio-cycloalkyl and substituted alkylthio-cycloalkyl.

In a preferred embodiment a ring is formed using R3 and R4.

In a further preferred embodiment for X2 and for X6 individually and independently R3 is selected from the group comprising phenyl, substituted phenyl, benzyl, substituted benzyl, 1,1-diphenylmethyl, substituted 1,1-diphenylmethyl, naphthylmethyl, substituted naphthylmethyl, thienylmethyl, substituted thienylmethyl, benzothienylmethyl, substituted benzothienylmethyl, imidazolylmethyl, substituted imidazolylmethyl, indolylmethyl and substituted indolylmethyl.

In an embodiment for X5 and for X7 individually and independently R3 is selected from the group comprising C3-C5-alkyl, substituted C3-C5-alkyl, C5-C7-cycloalkyl, substituted C5-C7-cycloalkyl, C5-C7-cycloalkylmethyl, substituted C5-C7-cycloalkylmethyl, cycloalkylethyl, substituted cycloalkylethyl, benzyl, substituted benzyl, phenylethyl, naphthylmethyl, thienylmethyl, propenyl, propinyl, methylthioethyl, imidazolylmethyl, substituted imidazolylmethyl, indolylmethyl and substituted indolylmethyl.

In another embodiment, X2 is an amino acid derivative of an amino acid selected from the group comprising phenylalanine, 2-fluoro-phenylalanine, 3-fluoro-phenylalanine, 4-fluoro-phenylalanine, 2-chlorophenylalanine, 3-chlorophenylalanine, 1-naphthylalanine, 2-thienylalanine, 3-thienylalanine, 3-3-diphenylalanine, tyrosine, tryptophane, histidine and respective derivatives thereof;

Or X2 and X1, taken together, are $PhCH_2CH_2CO$ or $PhCH_2$;

X6 is an amino acid derivtive of an amino acid selected from the group comprising tryptophane, phenylalanine, tyrosine, histidine, 1-naphthylalanine, bezothenylalanine, 2-aminoindan2-2-carboxylic acid, 2-thienylalanine, 3-thienylalanine, 2-fluoro-phenylalanine, 3-fluoro-phenylalanine, 4-fluoro-phenylalanine, 2-chlorophenylalanine, 3-chlorophenylalanine, 4-chlorophenylalanine and the respective derivatives thereof,

X5 is an amino acid derivative of an amino acid selected from the group comprising D-cyclohexylalanine, D-cyclohexylglycine, D-homo-cyclohexylalanine, and the respective dervatives thereof,

X7 is an amino acid derivative of an amino acid selected from the group comrpising norvaline, norleucine, homo-leucine, leucine, isoleucine, valine, cysteine, cysteine (Me), cysteine (Et), cysteine (Pr), methionine, allyl glycine, propargylglycine, cyclohexylglycine, cyclohexylalanine, phenylalanine, tyrosine, tryptophane, histidine, 1-naphthylalanine, 2-thienylalanine, 3-thienylalanine and respective derivatives thereof.

In a still further embodiment X1 and/or X4 comprise one or more groups that improve water solubility, whereby the water solubility improving group is selected from the group comprising hydroxy, keto, carboxamido, ether, urea, carbamate, amino, substituted amino, guanidino, pyridyl and carboxyl.

In a seventh aspect of the invention the problem is solved by a compound, preferably a C5a receptor antagonist, having the following structure:

$$X1\text{—}X2\text{—}X3\text{—}X4\text{—}X5\text{—}X6\text{—}X7\text{—}X8 \quad \text{(II)}$$

, whereby X1-X3 and X5-X8 are defined in one of the claims 17-26 and whereby

X4 is a cyclic or a non-cyclic amino acid, whereby the cyclic amino acid is selected from the group comprising proline, pipecolic acid, azetidine-2-carbonic acid, tetrahydroisoquinoline-3-carboxylic acid, tetrahydroisoquinoline-1-carboxylic acid, octahydroindole-2-carboxylic acid, 1-aza-bicyclo-[3.3.0]-octane-2-carboxylic acid, 4-phenyl-pyrrolidine-2-carboxylic acid, cis-Hyp

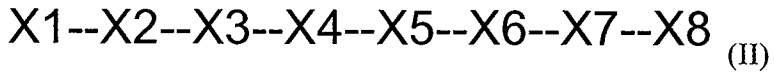
and trans-Hyp, and the non-cyclic amino acid is selected from the group comprising Ser, Gln, Asn, Cys($O_2CH_2CH_2CONH_2$), Arg, Hyp($COCH_2OCH_2CH_2OCH_2CH_2OCH_3$), Hyp(CONH-$CH_2CH(OH)$-$CH_2OH$) and respective derivatives thereof and respective analogs thereof; and

the connecting lines – in formula (I) represent chemical bonds, whereby preferably the chemical bond is preferably selected from the group comprising covalent bonds, ionic bonds and coordinative bonds, whereby preferably the bond is a chemical bond and more preferably the chemical bond is a bond selected from the group comprising amide bonds, disulfide bonds, ether bonds, thioether bonds, oxime bonds and aminotriazine bonds.

In an embodiment the derivatives and/or analogues are such that individual or several hydrogen atoms may be substituted.

In an embodiment amino acids are preferably selected from the group comprising proline, Pipecolic acid, azetidine-2-carboxylic acid, tetrahydroisoquinoline-3-carboxylic acid, tetrahydroisoquinoline-1-carboxylic acid, octahydroindole-2-carboxylic acid, 1-aza-bicyclo-[3.3.0]-octane-2-carboxylic acid, 4-phenyl-pyrrolidine-2-carboxylic acid, Hyp, Ser, Gln, Asn, Cys($O_2CH_2CH_2CONH_2$) and Arg.

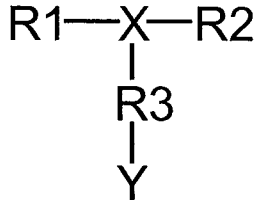
In an eightth aspect of the invention the problem is solved by a compound, preferably a C5a receptor antagonist, having the following structure:



(II)

, whereby X1-X2 and X4-X8 are defined as in one of claims 19 to 29 and whereby

X3 has the following structure:



(IV),

whereby

X is C(R4) or N,

R1 is optionally present and if R1 is present it is a radical selected from the group comprising >N-R1B, >C(R1B)(R1C) and >O, whereby R1B and R1C are individually and independently selected from the group comprising H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, arylakyl, substituted arylalkyl, cycloalkylalkyl and substituted cycloalkylalkyl;

R2 is optionally present and if R2 is present it is a radical selected from the group comprising C=O, C=S, SO_2, PO(OH), B(OH), CH_2, CH_2CO, CHF and CF_2;

R4 is a radical, whereby the radical is selected from the group comprising H, F, CH_3, CF_3, alkyl and substituted alkyl;

the binding of structure (IV) to the moieties X2 and X4 preferably takes place via R1 and R2;

R3 is a radical selected from the group comprising H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkylalkyl, substituted cycloalkylalkyl, heterocyclyl, substituted heterocyclyl, heterocyclylalkyl, substituted heterocyclylalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, acyl, substituted acyl, alkoxyalkyl, substituted alkoxyalkyl, aryloxyalkyl, substituted aryloxyalkyl, sulfhydrylalkyl, substituted sulfhydrylalkyl, hydroxyalkyl, substituted hydroxyalkyl, carboxyalkyl, substituted carboxyalkyl, carboxamidoalkyl, substituted carboxamidoalkyl, carboxyhydrazinoalkyl, ureidoalkyl aminoalkyl, substituted aminoalkyl, guanidinoalkyl and substituted guanidinoalkyl;

Y is optionally present and if present is a radical that is selected from the group comprising H, -N(YB1)-CO-YB2, -N(YB1)-CO-N(YB2)(YB3), -N(YB1)-C(N-YB2)-N(YB3)(YB4), -N(YB1)(YB2), -N(YB1)-SO_2-YB2, O-YB1, S-YB1, -CO-YB1, -CO-N(YB1)(YB2) and -C=N-O-YB1, whereby YB1, YB2, YB3 and YB4 are individually and independently selected from the group comprising H, CN, NO_2, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, arylakyl, substituted arylalkyl, cycloalkylalkyl and substituted cycloalkylalkyl.

In an embodiment R3 is a radical having the structure

$-(CH_2)_m-Y$ (V)

or

$-(CH_2)_m-C_6H_4-Y$ (VI) ist

, whereby

m is 1, 2, 3 or 4;

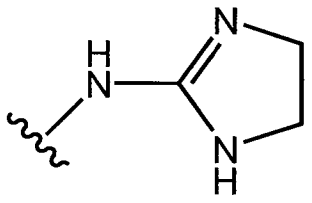
Y is N(R3b)(R3c) or -N(YB1)-C(N-YB2)-N(YB3)(YB4), whereby R3b, R3c, YB1, YB2, YB3 and YB4 are individually and independently selected from the group comprising H, CN and alkyl.

In an embodiment a ring is formed between each two groups, whereby the groups are individually and independently selected from the group comprising YB1, YB2, YB3 and YB4.

In a further embodiment the ring is formed by YB2 and YB3.

In a particularly preferred embodiment Y is

$-NH_2$

or  (IX).

In an embodiment of any aspect of the present invention, the compound is one of the following compounds:

No.	Compound
1	Ac-Phe-[Orn-Pro-cha-Trp-Phe]
2	Ac-Phe-[Orn-Hyp-cha-Trp-Phe]
3	$HOCH_2(CHOH)_4$-C=N-O-CH_2-CO-Phe-[Orn-Pro-cha-Trp-Nle]
4	X-Phe-[Orn-Pro-cha-Trp-Nle]; X = 2-acetamido-1-methyl-glucuronyl
5	Ac-Phe-[Orn-Hyp($COCH_2OCH_2CH_2OCH_2CH_2OCH_3$)-cha-Trp-Nle]
6	Ac-Phe-[Orn-Hyp(CONH-$CH_2CH(OH)$-CH_2OH)-cha-Trp-Nle]
20	Ac-Phe-[Orn-Pro-cha-Trp-Ecr]
28	Ac-Phe-[Orn-Pro-cha-Trp-Nle]
29	Ac-Phe-[Orn-Pro-cha-Trp-Met]
31	Ac-Phe-[Orn-Pro-cha-Trp-Nva]
32	Ac-Phe-[Orn-Pro-cha-Trp-Hle]
33	Ac-Phe-[Orn-Pro-cha-Trp-Eaf]
34	Ac-Phe-[Orn-Pro-cha-Trp-Ebd]
35	Ac-Phe-[Orn-Pro-cha-Trp-Eag]
36	Ac-Phe-[Orn-Pro-cha-Trp-Pmf]
37	Ac-Phe-[Orn-Pro-cha-Trp-2Ni]
38	Ac-Phe-[Orn-Pro-cha-Trp-Thi]
41	Ph-CH_2-CH_2-CO-[Orn-Pro-cha-Trp-Nle]
42	H-Phe-[Orn-Pro-cha-Trp-Nle]
43	Ac-Lys-Phe-[Orn-Pro-cha-Trp-Nle]
44	H-Phe-[Orn-Ser-cha-Trp-Nle]
51	Ac-Phe-Orn-Pro-cha-Trp-Phe-NH_2
52	Ac-Phe-Orn-Aze-cha-Bta-Phe-NH_2
53	Ac-Phe-Orn-Pro-cha-Bta-2Ni-NH_2
54	Ac-Phe-Orn-Pro-cha-Bta-Cha-NH_2
55	Ac-Phe-Orn-Pip-cha-Trp-Phe-NH_2
56	Ph-CH_2-[Orn-Pro-cha-Trp-Nle]

57	Ph-CH_2-[Orn-Pro-cha-Trp-Phe]
58	Ac-Phe-[Orn-Pro-cha-Trp-1Ni]
59	Ph-CH(OH)-CH_2-CO-[Orn-Pro-cha-Trp-Nle]
61	Ac-Phe-Orn-Pro-cha-Trp-Phe-NH_2
62	Ac-Phe-Orn-Pro-cha-Bta-Phe-NH_2
64	Ac-Phe-Orn-Pro-cha-Trp-2Ni-NH_2
65	Ac-Phe-Orn-Pro-cha-Trp-Cha-NH_2
66	Ac-Thi-Orn-Aze-cha-Bta-Phe-NH_2
67	Ac-Thi-Orn-Pip-cha-Bta-Phe-NH_2
68	Ac-Phe-Orn-Pro-cha-Trp-Eap-NH_2
69	Me_2-Phe-Orn-Pro-cha-Trp-Phe-NH_2
70	Ph_2-CH-CH_2-CO-Orn-Pro-cha-Trp-Phe-NH_2
71	Ac-Ebw-Orn-Pro-cha-Trp-Phe-NH_2
72	Ac-Phe-Orn-Pro-cha-Trp-NH-CH_2-CH_2-Ph
73	Ac-Phe-Orn-Aze-cha-Bta-NH-CH_2-CH_2-Ph
74	H-Phe-Orn-Pro-cha-Trp-Phe-NH_2
75	H-Me-Phe-Orn-Pro-cha-Trp-Phe-NH_2
76	Bu-NH-CO-Phe-Orn-Pro-cha-Trp-Phe-NH_2
77	Ac-Thi-Orn-Pro-cha-Trp-Phe-NH_2
78	Ac-Ebw-Orn-Pro-cha-Trp-Phe-NH_2
79	Ac-Phe-Orn-Ala-cha-Trp-Phe-NH_2
80	Ac-Phe-Orn-Pro-cha-Trp-Thi-NH_2
81	Ac-Phe-Orn-Aze-cha-Pcf-Phe-NH_2
82	Ac-Phe-Orn(Ac)-Pro-cha-Trp-Phe-NH_2
83	Ac-Phe-Orn-Aze-cha-Trp-Phe-NH_2
84	Ac-Phe-Trp-Pro-cha-Trp-Phe-NH_2
85	Ph-NH-CO-Phe-Orn-Pro-cha-Trp-Phe-NH_2
86	Bu-O-CO-Phe-Orn-Pro-cha-Trp-Phe-NH_2
87	Ac-Phe-Lys-Pro-cha-Trp-Phe-NH_2
88	Ac-Phe-Arg-Pro-cha-Trp-Phe-NH_2
89	Ac-Phe-Gln-Pro-cha-Trp-Phe-NH_2
92	Ac-Phe-Orn-Pip-cha-Trp-Phe-NH_2
93	Ac-Phe-Orn-Hyp-cha-Trp-Phe-NH_2

94	Ac-Phe-Orn-Pro-cha-Trp-1Ni-NH_2
95	Ac-Phe-Orn-Aze-cha-Bta-Phe-NH-Me
96	CH_3-SO_2-Phe-Orn-Aze-cha-Bta-Phe-NH_2
99	Ac-Phe-Orn-Aze-cha-Pff-Phe-NH_2
100	Ac-Phe-Orn-Aze-cha-Mcf-Phe-NH_2
101	Ac-Phe-Orn(Ac)-Aze-cha-Bta-Phe-NH_2
102	Ac-Ebw-Orn-Pro-cha-Trp-Phe-NH_2
103	Ac-Phe-Trp-Pro-cha-Trp-Phe-NH_2
104	Ac-Phe-Arg-Pro-cha-Trp-Phe-NH_2
105	Ac-Phe-Orn-Pip-cha-Trp-Phe-NH_2
106	3PP-Orn-Aze-cha-Bta-Phe-NH_2
107	Ac-Phe-Orn-Tic-cha-Trp-Phe-NH_2
108	Ac-Phe-Orn-Ser-cha-Trp-Phe-NH_2
109	Ac-Phe-Orn-Pro-chg-Trp-Phe-NH_2
110	Ac-Phe-Orn-Pro-hch-Trp-Phe-NH_2
111	Ac-Phe-Orn-Pro-cha-Trp-Phg-NH_2
112	Ac-Phe-Bta-Aze-cha-Bta-Phe-NH_2
113	Ac-Phe-Trp-Pro-cha-Bta-Phe-NH_2
115	Ac-Phe-Orn-Pip-cha-Trp-Phe-OH
116	Ac-Phe-Orn-Tic-cha-Trp-Phe-OH
117	Ac-Phe-Orn-Ser-cha-Trp-Phe-OH
118	Ac-Phe-Orn-Pro-chg-Trp-Phe-OH
119	Ac-Phe-Eec-Pro-cha-Bta-Phe-NH_2
120	Ac-Phe-Nle-Pro-cha-Bta-Phe-NH_2
121	Ac-Phe-Har-Pro-cha-Bta-Phe-NH_2
122	Ac-Phe-Arg-Pro-cha-Bta-Phe-NH_2
123	Ac-Phe-Cys(Acm)-Pro-cha-Bta-Phe-NH_2
124	Ac-Phe-Mpa-Pro-cha-Bta-Phe-NH_2
125	Ac-Eby-Orn-Pro-cha-Bta-Phe-NH_2
126	Ac-Phg-Orn-Pro-cha-Bta-Phe-NH_2
127	Ac-Phe-Paf-Pro-cha-Bta-Phe-NH_2
128	H_2N-CO-Phe-Orn-Pro-cha-Bta-Phe-NH_2
129	Me-O-CO-Phe-Orn-Pro-cha-Bta-Phe-NH_2

130	(-CO-CH_2-NH-CO-)-Phe-Orn-Pro-cha-Bta-Phe-NH_2
132	Ac-Phe-Orn-Pro-hch-Trp-Phe-OH
133	(-CO-CH_2-CH_2-CO-)-Phe-Orn-Pro-cha-Bta-Phe-NH_2
134	^{t}Bu-CO-Phe-Orn-Pro-cha-Bta-Phe-NH_2
135	Ac-Lys-Phe-Orn-Aze-cha-Bta-Phe-NH_2
136	Ac-Gly-Phe-Orn-Aze-cha-Bta-Phe-NH_2
137	Ac-Arg-Phe-Orn-Aze-cha-Bta-Phe-NH_2
138	Ac-His-Phe-Orn-Aze-cha-Bta-Phe-NH_2
139	Ac-Ser-Phe-Orn-Aze-cha-Bta-Phe-NH_2
140	Ac-Guf-Phe-Orn-Aze-cha-Bta-Phe-NH_2
141	Ac-Dab-Phe-Orn-Aze-cha-Bta-Phe-NH_2
142	FH_2C-CO-Phe-Orn-Pro-cha-Bta-Phe-NH_2
143	Ac-Phe-Orn(Et_2)-Pro-cha-Trp-Phe-NH_2
144	Ac-Phe-[Orn-Hyp-cha-Trp-Nle]
145	3PP-[Orn-Hyp-cha-Trp-Nle]
146	Ac-Phe-[Orn-Pro-cha-Trp-Tyr]
147	Ac-Phe-[Orn-Pro-omf-Trp-Nle]
149	Ac-Phe-Orn-Pro-hle-Bta-Phe-NH_2
150	Ac-Phe-Arg(CH_2-CH_2)-Pro-cha-Bta-Phe-NH_2

In a ninth aspect of the invention the problem is solved by a pharmaceutical composition comprising at least one compound according to any of the aspects of the present invention and additionally a pharmaceutically acceptable carrier.

In a tenth aspect of the invention the problem is solved by the use of at least one of the compounds of any of the aspect sof the present invention for the manufacture of a medicament.

In an embodiment the medicament is used for the prevention and/or treatment of a condition associated with complement activation and/or where the inhibition of the complement system leads to a relief of the symptoms.

In a further embodiment the condition and/or the symptoms to be treated are selected from the group comprising rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis,

psoriasis, septic shock, asthma, vasculitis, myocarditis, dermatomyositis, inflammatory bowel disease (IBD), pemphigus, myasthenia gravis, acute respiratory insufficiency, stroke, myocardial infarction, reperfusion injury, and acute injuries of the central nervous system.

In an eleventh aspect the problem is solved according to the invention by the use of at least one compound according to any of the aspects fo the present invention for the prevention and/or support of surgery.

In an embodiment of the tenth aspect of the present invention the medicament is used for the prevention and/or support of surgery.

In another embodiment of the tenth aspect the medicament is used for the prevention and/or support and/or after-care of surgery, whereby surgery is selected from the group comprising CABG, PACT; PTA; MidCAB; OPCAB, thrombolysis and vascular occlusion (clamping).

In a still further embodiment of the tenth aspect, the medicament is used for a thrombolytic treatment.

In a still further embodiment of the tenth aspect the medicament, as aprt fo a dialysis treatment, is optionally used before, during or after the treatment.

In a further aspect, the compounds according to the invention are used for the manufacture of a medicament for the support of surgery an/or after-care of a disease, whereby the disease is selected from the group comprising myocardial infarction, CABG(Coronary Artery Bypass Surgery), PTCA (Percutaneous Transluminal Coronary Angioplasty); PTA (Percutaneous Transluminal Angioplasty); MidCAB (Minimally Invasive Direct Coronary Artery Bypass) OPCAB (Off Pump Coronary Artery Bypass), stroke, thrombolysis, vascular acclusion and burn.

In a further embodiment, the compounds according to the invention may be used for the manufacture of a medicament for the support of a thrombolytic treatment. In a further embodiment, the compounds according to the invention are used for dialysis or the manufacture of a medicament, respectively, used as part of a dialysis treatment optionally before, during or after the treatment. This is done to avoid or reduce negative effects associated with extracorporeal circulation.

In a still further aspect the present invention is related to a method for the treatment of patients, whereby the method comprises the administration of one or several of the compounds according to the present invention. The treatment may be a treatment in the narrower sense, however, also includes a preventive treatment and a secondary treatment.

The patient to be treated is preferably a mammal, more preferably a domestic farming animal, sports animal and pet, and most preferably a human being. In a preferred embodiment the patient is a patient in need of such treatment. In a further preferred embodiment the patient is suffering from one of the above mentioned diseases for the treatment of which the compounds according to the present invention may be used.

The invention thus provides for the first time such antagonists for the C5a receptor, that overcome the inherent pharmacological disadvantages of the antagonistic peptides of the prior art which contain a positive charge.

The invention is based on the surprising finding, that in contrast to the technical teaching of the prior art, also antagonists for the C5a receptor can be obtained which, under physiological conditions, especially at a pH of 7.4, do not have a positive net charge and/or whose C-terminal amino acid does not possess a positive charge under physiological conditions.

The positive charge in peptides can be very disadvantageous from a pharmacological point of view. Positive charges can, e. g., lead to histamine release and cause lower membrane permeability (see example 15). Therefore it is particularly desired to develop a peptidic antagonist that does not possess a positive net charge (in the following also referred to as compound).

The compounds which are disclosed in the present invention were tested in a primary assay for their IC_{50} values in a functional assay system. Preferably all compounds, peptides and peptidomimetics are regarded to have noteworthy inhibitory activity in the sense of the present invention, that have an IC_{50} value of less than 200 nM in a functional assay system as described in example 1.

In particular the compounds of the invention are C5a receptor antagonists. Even more preferably they are peptides or peptidomimetics. Furthermore the invention is based on the surprising

finding, that the compounds which are used in accordance with the present invention as C5a receptor antagonists posses an uncharged C-terminal amino acid, amino acid derivative or amino acid analog.

In connection with the present invention, however, it was also surprisingly found that linear, thus structurally flexible, peptides can be as potent inhibitors as structurally fixed cyclic peptides. This is subject to substitution of the C-terminal charged arginine by hydrophobic amino acids, amino acid derivatives or amino acid analogs. Examples for such linear peptidic inhibitors according to the invention are in particular the compounds shown in the following table:

51	Ac-Phe-Orn-Pro-cha-Trp-Phe-NH2
52	Ac-Phe-Orn-Aze-cha-Bta-Phe-NH2
53	Ac-Phe-Orn-Pro-cha-Bta-2Ni-NH2
54	Ac-Phe-Orn-Pro-cha-Bta-Cha-NH2
55	Ac-Phe-Orn-Pip-cha-Trp-Phe-NH2
61	Ac-Phe-Orn-Pro-cha-Trp-Phe-NH2
62	Ac-Phe-Orn-Pro-cha-Bta-Phe-NH2
64	Ac-Phe-Orn-Pro-cha-Trp-2Ni-NH2
65	Ac-Phe-Orn-Pro-cha-Trp-Cha-NH2
66	Ac-Thi-Orn-Aze-cha-Bta-Phe-NH2
67	Ac-Thi-Orn-Pip-cha-Bta-Phe-NH2
68	Ac-Phe-Orn-Pro-cha-Trp-Eap-NH2
69	Me2-Phe-Orn-Pro-cha-Trp-Phe-NH2
70	Ph2-CH-CH2-CO-Orn-Pro-cha-Trp-Phe-NH2
71	Ac-Ebw-Orn-Pro-cha-Trp-Phe-NH2
72	Ac-Phe-Orn-Pro-cha-Trp-NH-CH2-CH2-Ph
73	Ac-Phe-Orn-Aze-cha-Bta-NH-CH2-CH2-Ph
74	H-Phe-Orn-Pro-cha-Trp-Phe-NH2
75	H-Me-Phe-Orn-Pro-cha-Trp-Phe-NH2
76	Bu-NH-CO-Phe-Orn-Pro-cha-Trp-Phe-NH2

77	Ac-Thi-Orn-Pro-cha-Trp-Phe-NH2
78	Ac-Ebw-Orn-Pro-cha-Trp-Phe-NH2
79	Ac-Phe-Orn-Ala-cha-Trp-Phe-NH2
80	Ac-Phe-Orn-Pro-cha-Trp-Thi-NH2
81	Ac-Phe-Orn-Aze-cha-Pcf-Phe-NH2
82	Ac-Phe-Orn(Ac)-Pro-cha-Trp-Phe-NH2
83	Ac-Phe-Orn-Aze-cha-Trp-Phe-NH2
84	Ac-Phe-Trp-Pro-cha-Trp-Phe-NH2
85	Ph-NH-CO-Phe-Orn-Pro-cha-Trp-Phe-NH2
86	Bu-O-CO-Phe-Orn-Pro-cha-Trp-Phe-NH2
87	Ac-Phe-Lys-Pro-cha-Trp-Phe-NH2
88	Ac-Phe-Arg-Pro-cha-Trp-Phe-NH2
89	Ac-Phe-Gln-Pro-cha-Trp-Phe-NH2
92	Ac-Phe-Orn-Pip-cha-Trp-Phe-NH2
93	Ac-Phe-Orn-Hyp-cha-Trp-Phe-NH2
94	Ac-Phe-Orn-Pro-cha-Trp-1Ni-NH2
95	Ac-Phe-Orn-Aze-cha-Bta-Phe-NH-Me
96	CH3-SO2-Phe-Orn-Aze-cha-Bta-Phe-NH2
99	Ac-Phe-Orn-Aze-cha-Pff-Phe-NH2
100	Ac-Phe-Orn-Aze-cha-Mcf-Phe-NH2
101	Ac-Phe-Orn(Ac)-Aze-cha-Bta-Phe-NH2
102	Ac-Ebw-Orn-Pro-cha-Trp-Phe-NH2
103	Ac-Phe-Trp-Pro-cha-Trp-Phe-NH2
104	Ac-Phe-Arg-Pro-cha-Trp-Phe-NH2
105	Ac-Phe-Orn-Pip-cha-Trp-Phe-NH2
106	3PP-Orn-Aze-cha-Bta-Phe-NH2
107	Ac-Phe-Orn-Tic-cha-Trp-Phe-NH2
108	Ac-Phe-Orn-Ser-cha-Trp-Phe-NH2
109	Ac-Phe-Orn-Pro-chg-Trp-Phe-NH2
110	Ac-Phe-Orn-Pro-hch-Trp-Phe-NH2
111	Ac-Phe-Orn-Pro-cha-Trp-Phg-NH2
112	Ac-Phe-Bta-Aze-cha-Bta-Phe-NH2

113	Ac-Phe-Trp-Pro-cha-Bta-Phe-NH2
115	Ac-Phe-Orn-Pip-cha-Trp-Phe-OH
116	Ac-Phe-Orn-Tic-cha-Trp-Phe-OH
117	Ac-Phe-Orn-Ser-cha-Trp-Phe-OH
118	Ac-Phe-Orn-Pro-chg-Trp-Phe-OH
119	Ac-Phe-Eec-Pro-cha-Bta-Phe-NH2
120	Ac-Phe-Nle-Pro-cha-Bta-Phe-NH2
121	Ac-Phe-Har-Pro-cha-Bta-Phe-NH2
122	Ac-Phe-Arg-Pro-cha-Bta-Phe-NH2
123	Ac-Phe-Cys(Acm)-Pro-cha-Bta-Phe-NH2
124	Ac-Phe-Mpa-Pro-cha-Bta-Phe-NH2
125	Ac-Eby-Orn-Pro-cha-Bta-Phe-NH2
126	Ac-Phg-Orn-Pro-cha-Bta-Phe-NH2
127	Ac-Phe-Paf-Pro-cha-Bta-Phe-NH2
128	H2N-CO-Phe-Orn-Pro-cha-Bta-Phe-NH2
129	Me-O-CO-Phe-Orn-Pro-cha-Bta-Phe-NH2
130	(-CO-CH2-NH-CO-)-Phe-Orn-Pro-cha-Bta-Phe-NH2
132	Ac-Phe-Orn-Pro-hch-Trp-Phe-OH
133	(-CO-CH2-CH2-CO-)-Phe-Orn-Pro-cha-Bta-Phe-NH2
134	tBu-CO-Phe-Orn-Pro-cha-Bta-Phe-NH2
135	Ac-Lys-Phe-Orn-Aze-cha-Bta-Phe-NH2
136	Ac-Gly-Phe-Orn-Aze-cha-Bta-Phe-NH2
137	Ac-Arg-Phe-Orn-Aze-cha-Bta-Phe-NH2
138	Ac-His-Phe-Orn-Aze-cha-Bta-Phe-NH2
139	Ac-Ser-Phe-Orn-Aze-cha-Bta-Phe-NH2
140	Ac-Guf-Phe-Orn-Aze-cha-Bta-Phe-NH2
141	Ac-Dab-Phe-Orn-Aze-cha-Bta-Phe-NH2
142	FH2C-CO-Phe-Orn-Pro-cha-Bta-Phe-NH2
143	Ac-Phe-Orn(Et2)-Pro-cha-Trp-Phe-NH2
149	Ac-Phe-Orn-Pro-hle-Bta-Phe-NH2
150	Ac-Phe-Arg(CH2-CH2)-Pro-cha-Bta-Phe-NH2

The linear peptides known from the prior art such as Finch et al. 1999 Journal of Medicinical Chemistry 42: 1965-1974; Wong et al. 1999 IDrugs 2: 686-693, US 4,692,511, US 5,663,148, WO 90/09162, WO 92/11858, WO 92/12168, WO 92/21361, WO 94/07518, WO 94/07815, WO 95/25957, WO 96/06629, WO 99/00406, and WO 99/13899 are in general significantly worse antagonists of C5a compared to cyclic peptides which are described in WO 99/00406 (e.g. Ac-Phe-[Lys-Pro-cha-Trp-arg], Ac-Phe-[Orn-Pro-cha-Trp-arg], Ac-Phe-[Orn-Pro-cha-Trp-Arg], Ac-Phe-[Lys-Pro-cha-Trp-Arg]). The in terms of antagonistic activity most active linear peptide described in WO 99/00406 has the sequence Me-Phe-Lys-Pro-cha-Trp-arg and an IC_{50} of 0.085 µM (measured with the cellular myeloperoxidase release assay with human PMNs). In contrast thereto, the comparable cyclic peptide Ac-Phe-[Lys-Pro-cha-Trp-arg] (also from WO 99/00406) has an IC_{50} of 0.012 µM. In WO 99/00406 it is mentioned that the decreased structural flexibility of the cyclic peptide leads to the decrease, i.e. an improvement of the IC_{50}. This is reflected in the development of cyclic – meaning least flexible – inhibitors like Ac-Phe-[Lys-Pro-cha-Trp-arg] and Ac-Phe-[Orn-Pro-cha-Trp-Arg].

Thus, the inventors intentionally departed from the understanding of the prior art regarding at least one aspect of the present invention and accordingly provide a new class of compounds which can be used as C5aR antagonists.

The present invention describes for the first time peptidic and peptidomimetic C5aR antagonists having IC50s < 200 nM, which do not have a positive net charge under physiological pH values (pH 7.4) and/or which C-terminal amino acid does not carry a positive charge. The IC_{50} value is determined with a functional assay (Köhl 1997 The Anaphylatoxins. In: Dodds, A.W., Sim, R.B. (Eds.), Complement: A Practical Approach. Oxford, pp. 135-163). The compounds according to this invention can therefore be used as C5aR antagonists, especially under physiological conditions.

The compounds according to this invention do underline the finding that a suitable hydrophobic substitution of an aliphatic, aromatic or heteroaromatic kind can replace the C-terminal arginine of C5aR binding peptides.

Another feature of the compounds according to this invention, especially of the peptides and peptidomimetics, is the absence of agonistic activity in a cellular assay up to a concentration of at least 1430 nM. Example 12 shows by way of example results from measurements with

selected peptides according to the present invention using a method for determinating C5aR agonistic activities. Obviously, the compounds according to the present invention do not show any agonistics activity up to the highest concentration used. Within the present invention the following compounds in accordance with the present invention are examples for peptides in accordance with the present invention which are pure antagonists: $HOCH_2(CHOH)_4$-C=N-O-CH_2-CO-Phe-[Orn-Pro-cha-Trp-Nle], Ph-CH_2-CH_2-CO-[Orn-Pro-cha-Trp-Nle], Ac-Phe-[Orn-Hyp-cha-Trp-Phe], H-Phe-[Orn-Pro-cha-Trp-Phe], Ac-Phe-[Orn-Pro-cha-Trp-Phe], Ac-Lys-Phe-[Orn-Pro-cha-Trp-Nle], H-Phe-[Orn-Pro-cha-Trp-Nle], H-Phe-[Orn-Ser-cha-Trp-Nle], Ac-Phe-[Orn-Pro-cha-Trp-Eaf], Ac-Phe-Orn-Pro-cha-Trp-Phe-NH_2, Ac-Phe-Orn-Pro-cha-Bta-Phe-NH_2, Ac-Ebw-Orn-Pro-cha-Trp-Phe-NH_2, Ac-Phe-Orn-cha-cha-Bta-Phe-NH_2, Ac-Phe-Arg-Pro-cha-Trp-Phe-NH_2, Ac-Phe-Orn-Pip-cha-Trp-Phe-NH_2, Ac-Phe-Orn-Aze-cha-Trp-Phe-NH_2, Ac-Phe-Trp-Pro-cha-Trp-Phe-NH_2, Ac-Thi-Orn-Pip-cha-Bta-Phe-NH_2, Ac-Phe-Orn-Pro-hle-Bta-Phe-NH_2, Ac-Phe-Arg(CH_2-CH_2)-Pro-cha-Bta-Phe-NH_2.

For a detailed analysis of the C5aR antagonism and the development of a pharmacophore model of the compound Ac-Phe-[Orn-Pro-cha-Trp-Arg] the amino acids Phe, Trp and Arg were replaced by L-alanine, Pro was replaced by NMe-alanine and cha was replaced by D-alanine (single substitutions). The resulting peptides were analysed with a functional assay with regard to their C5aR antagonistic activity (example 11). From this approach it is apparent that the substitution of the amino acid side chains of Trp, cha, and Phe by methyl groups results in a pronounced loss of activity (IC_{50} values > 30 µM). In contrast to that the activity of the antagonist Ac-Phe-[Orn-Pro-cha-Trp-Arg] is comparable to the activity of the molecule having Pro replaced by NMeAla (IC_{50} = 20 nM compared to 25 nM). The substitution of Ala for Arg also leads to a significant loss in activity (IC_{50} = 16 nM to IC_{50} = 5.6 µM) which is nevertheless less pronounced than for the substitution of Trp and Phe.

Additional substitutions at the peptide Ac-Phe-[Orn-Pro-cha-Trp-Arg] and similar compounds lead to a number of peptides and peptidomimetics, respectively, which, surprisingly, have noteworthy inhibitory activities (example 11). Especially the following peptides show noteworthy inhibitory activity: Ac-Phe-[Orn-Pro-cha-Trp-Phe], Ac-Phe-[Orn-Hyp-cha-Trp-Phe], Ac-Phe-[Orn-Pro-cha-Trp-Paf], Ac-Phe-[Orn-Pro-cha-Trp-Ecr], Ac-Phe-[Orn-Pro-cha-Trp-Ppa], Ac-Phe-[Orn-Pro-cha-Trp-Nle], Ac-Phe-[Orn-Pro-cha-Trp-Met], Ac-Phe-[Orn-Pro-cha-Trp-Nva], Ac-Phe-[Orn-Pro-cha-Trp-Hle], Ac-Phe-[Orn-Pro-cha-Trp-Eaf], Ac-Phe-[Orn-Pro-cha-Trp-Ebd], Ac-Phe-[Orn-Pro-cha-Trp-Eag], Ac-Phe-[Orn-Pro-cha-Trp-Pmf], Ac-Phe-[Orn-Pro-

cha-Trp-2Ni], Ac-Phe-[Orn-Pro-cha-Trp-Thi], Ac-Phe-[Orn-Pro-cha-Trp-Nle], Lys-Phe-[Orn-Pro-cha-Trp-Nle], Ac-Phe-[Orn-Ser-cha-Trp-Phe], $HOCH_2(CHOH)_4$-C=N-O-CH_2-CO-Phe-[Orn-Pro-cha-Trp-Nle], Ac-Phe-[Orn-Hyp($COCH_2OCH_2CH_2OCH_2CH_2OCH_3$)-cha-Trp-Phe], Ac-Phe-[Orn-Hyp($CONHCH_2COH(OH)CH_2OH$)-cha-Trp-Phe], Phenylpropionyl-[Orn-Pro-cha-Trp-Nle], Ac-Phe-Orn-Pro-hle-Bta-Phe-NH_2, Ac-Phe-Arg(CH_2-CH_2)-Pro-cha-Bta-Phe-NH_2.

The oral absorption of peptides is influenced by a variety of factors like size, charge, and hydrophobicity. Nevertheless, the oral availability of a peptide cannot be predicted a priori. In general, peptides are regarded to have poor oral availablity (Burton et al. 1996 Journal of Pharmaceutical Sciences 85: 1337-1340). A model for the estimation of the oral absorption is the measurement of the AB permeability through a monolayer of gut epithelial cells (e.g. CaCo2 or TC-7) (example15, Lennernäs 1997 Journal of Pharmacy and Pharmacology 49: 627-38). The compounds according to the invention which can be used as C5aR antagonists, show a significantly increased AB permeability due to the hydrophobic substitution of the C-terminal arginine. For example, the antagonist Ac-Phe-[Orn-Hyp-cha-Trp-Phe] has a surprisingly high permeability of $14.3x10^{-6}$ cm/s compared to the bad permeability of $0.52x10^{-6}$ of the charged antagonist Ac-Phe-[Orn-Pro-cha-Trp-Arg]. The high permeability is in terms of figures within a range close to the one of orally well available compounds. An example for an orally well available compound is Propanolol, which shows an AB permeability of $31.1x10^{-6}$ cm/s in this test by Lennernäs.

It is also within the present invention that the compounds according to the present invention have introduced groups at X1 and/or X4 which improve water solubility. Especially useful for improving water solubility is the introduction of groups which are able to have strong interactions with water and which are strongly solvatized. Frequently used groups are: hydroxy, keto, carboxamido, ether, urea, carbamate, amino, substituted amino, guanidino, pyridyl, carboxyl. The disclosed groups can explicitly be introduced at all positions at X1 and/or X4, and both one and several of the water solubility increasing groups can be introduced. Examples for the introduction of several groups are the attachments of carbohydrate residues and ethylene glycols.

Therefore, the present invention especially also includes peptidic and peptidomimetic C5aR antagonists, especially according to the present invention, the solubility of which is improved by additional modifications. Such modifications are known to the one skilled in the art and include,

for example, the introduction of the previously mentioned solubility improving groups. That this is an efficient method and, respectively, leads to highly active antagonists will be demonstraded by the following examples.

In accordance with example 13, compound **1** shows a solubility of 8% in aqueous HEPES buffer (pH 7.4). In contrast thereto, compound **40** has a solubility of 94% in HEPES buffer. Compound **2** which has an additional OH group compared to compound **1,** shows a solubility of 13%. By adding more complex hydrophilic groups as shown for compound **4**, the solubility is increased from 22% (compound **28**) to 84% (compound **4**). This is true although compound **4** is not charged. Thus it is ensured that the peptide and peptidomimetics according to the present invention, despite their hydrophobic character, can be converted into a well water-soluble form.

In the following some terms are set forth the meaning of which is to be used for embodiments of the present invention, in particular those which are set forth herein in more detail. Although these terms are occasionally referred to as definitions, the meaning of the various terms is not necessarily limited thereto.

The term "comprises" means, in preferred embodiments, that the respective structural element is included, but the structure is not limited to it.

The term "substituted" means, in preferred embodiments, that one or several hydrogen atoms of a group or a compound is/are replaced by a different atom, group of atoms, molecule or group of molecules. In connection therewith, such an atom, group of atoms, molecules and group of molecules itself/themselves is/are referred to as substituents or substitutions. A prerequisite for any substitution is that the customary normal valence of the atom is not exceeded, and that the substitution results in a stable compound. By the substitution of two hydrogen atoms a carbonyl group (C=O) can be generated. Carbonyl groups are preferably not present in aromatic moieties.

Substituents or substitutions can preferably be selected individually or in any combination from the group consisting of hydroxyl, alkoxyl, mercapto, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, arylalkoxy, heteroaryl, aryloxy, halogen, trifluoromethyl, difluoromethyl, cyano, nitro, azido, amino, aminoalkyl, carboxamido, -C(O)H, acyl, oxazolyl oxyacyl, carboxyl, carbamate, sulphonyl, sulfone amide and sulfuryl. Each substituent itself can be substituted further by one or several further substituents. This applies

particularly to alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl and aryloxy. Furthermore any definitions set forth herein apply also to substituents.

The term "alkyl" refers, in a preferred embodiment of the present invention, to a saturated aliphatic radical comprising from one to ten carbon atoms or a mono- or polyunsaturated aliphatic hydrocarbon radical comprising from two to twelve carbon atoms and at least one double and triple bond. The term "alkyl" includes both branched and unbranched alkyl groups. Unbranched alkyl groups having from one to eight carbon atoms are preferred. Unbranched alkyl groups having from one to six carbon atoms and branched alkyl groups having from three to six carbon atoms are particularly preferred. It should be understood that the term "alkyl" comprises any analogs which can be put together from combination terms of the prefix "alk" or "alkyl".

For example, the term "alkoxy" or "alkylthio" refers to an alkyl group which is linked by an oxygen or sulfur atom. "Alkanoyl" refers to an alkyl group which is linked by a carbonyl group (C=O).

The term "cycloalkyl" refers, in an embodiment of the present invention, to the cyclic derivatives of an alkyl group as defined above, which is optionally unsaturated and/or substituted. Saturated cycloalkyl groups are preferred, particularly those having from three to eight carbon atoms. Particularly preferred are cycloalkyl groups having three to six carbon atoms.

The term "aryl" refers, in an embodiment of the present invention, to an aromatic group having from 6 to 14 carbon atoms, whereby "substituted aryl" refers to aryl groups bearing one or more substituents.

Each of the above defined groups "alkyl", "cycloalkyl", and "aryl" comprise the respective halogenated derivatives, whereby the halogenated derivatives may comprise one or several halogen atoms. The halogenated derivatives comprise any halogen radical as defined in the following.

The term "halo" refers, in a preferred embodiment of the present invention, to a halogen radical selected from fluoro, chloro, bromo, and iodo. Preferred halo groups are fluoro, chloro and bromo.

The term "heteroaryl" refers, in an embodiment of the present invention, to a stable 5- to 8-membered, preferably 5- or 6-membered monocyclic or 8- to 11-membered bicyclic aromatic heterocyclic radical, whereby each heterocycle may consist of both carbon atoms and from 1 to 4 heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur. The heterocycle may be linked by any atom of the cycle such that a stable structure results. Within the present invention preferred heteroaryl radicals are, for example, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolizinyl, indolyl, isoindolyl, benzofuranyl, benzothienyl, indazolyl, benzimidazolyl, benzthiazolyl, benzoxazolyl, purinyl, quinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl and phenoxazinyl.

The term "heterocyclyl" refers, in an embodiment of the present invention, to a stable 5- to 8-membered, preferably 5- or 6-membered monocyclic or 8- to 11-membered bicyclic heterocyclic radical which is either saturated or unsaturated, but is not aromatic. Each heterocycle consists of both carbon atoms and from 1 to 4 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. The heterocycle may be linked by any atom of the cycle, which results in a stable structure. Preferred heterocyclic radicals within the present invention include, for example, pyrrolinyl, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, pyranyl, thiopyranyl, piperazinyl, indolinyl, azetidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrofuranyl, hexahydropyrimidinyl, hexahydropyridazinyl, 1,4,5,6-tetrahydropyrimidin-2-ylamine, dihydro-oxazolyl, 1,2-thiazinanyl-1,1-dioxide, 1,2,6-thiadiazinanyl-1,1-dioxide, isothiazolidinyl-1,1-dioxide and imidazolidinyl-2,4-dione.

When the terms "heterocyclyl", "heteroaryl" and "aryl" are used together with other expressions and terms, the above definitions are further applicable. For example, "aroyl" refers to a phenyl or naphthyl group linked to a carbonyl group (C=O).

Each aryl or heteroaryl compound also includes its partially or fully hydrogenated derivatives. For example, quinolinyl may also include decahydroquinolinyl and tetrahydroquinolinyl. Naphthyl may also include the hydrogenated derivatives such as tetrahydronaphthyl.

Within the present invention by the terms "nitrogen" or "N" and "sulfur" or "S" any oxidized derivative of nitrogen like nitrones, N-oxides or of sulfur like sulfoxides, sulfones and the quaternized forms of any basic nitrogen and HCl- or TFA-salts are included.

Radicals can be any of mono-, di-, tri-, and tetra-radicals. Because of this it is possible that the meaning of various terms slightly changes. For example, a di-radical described as "propyl", inevitably means "propyplene" (e.g. $-(CH_2)_3-$).

Any wording which specifies the limits of a range such as, e. g., "from 1 to 5" means any integer from 1 to 5, i. e. 1, 2, 3, 4 and 5. In other words, any range that is defined by two integers comprises both the two integers defining said limits of the definition and any integer comprised in said range.

The present invention also comprises all isotopes of atoms of the described compounds. Isotopes are atoms having the same atomic number but different mass numbers. For example, tritium and deuterium are isotopes of hydrogen. Examples for carbon isotopes are ^{11}C, ^{13}C and ^{14}C.

The term "energetically accessible conformer" means any conformer of a compound that falls within about a 20 kcal/mol window above the lowest energy conformation. In connection therewith, e. g., a Monte Carlo or systematic conformational search using MM2, MM3, or MMFF force fields as implemented in molecular modeling software such as MacroModel® v 7.0, Schrödinger Inc. Portland, Oregon, USA (http://www.schrodinger.com) or the like, can be used.

Amino acids are well-known to the ones skilled in the art and defined by the fact that a molecule comprises both an amino and a carboxylic acid group. Both natural and unnatural amino acids can be meant. Examples are α-, β-, and ω-amino acids, whereby preferably α-amino acids, more preferably α-L-amino-acids are used. In case an amino acid is not specified in more detail (e.g. "tryptophane"), both the L-and the D-form are meant.

A natural amino acid is an L-amino acid selected from the group glycine, leucine, isoleucine, valine, alanine, phenylalanine, tyrosine, tryptophane, aspartic acid, asparagine, glutamic acid, glutamine, cysteine, methionine, arginine, lysine, proline, serine, threonine and histidine.

An unnatural amino acid is a non proteinogenic amino acid, which includes, but is not limited to, D-amino acids, N-alkyl-amino acids, homo amino acids, α,α-disubstituted amino acids and dehydro amino acids.

Amino acid derivatives are compounds which result from amino acids by modifying the N and/or C-termus. Non-limiting examples are the conversion of the carboxy group to salts, esters, acylhydrazides, hydroxamic acids or amides, and the conversion of the amino group to amides, ureas, thioureas, thioamides, sulfonamides, phosphoric acid amides, boric acid amides or alkyl amines. Parts of compounds, which result from modifications of amino acids at the C and/or N-termini, can also be referred to as amino acid units.

Amino acid analogues are compounds, which result from amino acids by replacing the amino and/or carboxy group by other groups which can mimic them. Non-limiting examples are the incorporation of thioamides, ureas, thioureas, acylhydrazides, esters, alkyl amines, sulfonamides, phosphoric acid amides, ketones, alcohols, boronic acid amides, benzodiazepines and other aromatic or non-aromatic heterocycles (for a review see M. A. Estiarte, D. H. Rich in Burgers Medicinal Chemistry, 6th edition, volume 1, part 4, John Wiley & Sons, New York, 2002).

Aromatic amino acids are amino acids which comprise aryl or heteroaryl groups. Non-limiting examples are phenylalanine, tyrosine, histidine, tryptophane, homo-phenylalanine, homo-tyrosine, homo-histidine, homo- tryptophane, 1-naphtylalanine, 2-naphtylalanine, 2-thienylalanine, 3-thienylalanine, benzothienylalanine, furylalanine, thiazolylalanine, pyridylalanine, tetrahydroisochinoline-2-Carboxylic acid, 2-aminoindane-2-carboxylic acid, biphenylalanine, 3,3-diphenylalanine and corresponding D- and β-amino acids.

Hydrophobic amino acids are amino acids, which comprise hydrophobic alkyl-, cycloalkyl-, heterocyclyl, aryl or heteroaryl groups. Non-limiting examples are leucine, isoleucine, valine, phenylalanine, cysteine, methionine, proline, tryptophane, norleucine, norvaline, cyclohexyl alanine, cyclopentyl alanine, 1-naphtylalanine, 2-naphtylalanine, 2-thienylalanine, 3-thienylalanine, benzothienylalanine, allyl glycine, propargylglycine, 2-methyl-phenylalanine, 3-methyl-phenylalanine, 4-methyl-phenylalanine, homocyclohexylalanine, cyclohexyl glycine, n-cyclohexylglycine, octahydroindol-2-carboxylic acid and corresponding D- and β-amino acids.

The biological binding characteristics of an amino acid unit are those binding characteristics shown by the respective amino acid during the interaction with a biological molecule. Biological molecules are especially molecules exerting a biological function. Non-limiting examples of such biological molecules are protein- or peptide-based receptors.

Groups or units which mimic or imitate the biological binding characteristics of an amino acid, are defined as groups, which can establish with a receptor or interacting partner, preferably a biological receptor or a biological interaction partner, an interaction identical or similar to the amino acid itself. For the selection of such groups it is preferred to take into consideration those which are the most wide-spread ones in terms of most preferred interactions of the respective amino acids with biological receptors. For example, the oxygen atom of a carbonyl group of an amino acid can function as hydrogen bond acceptor, whereas the NH proton can establish interactions as hydrogen bond donor. Amino acids can additionally interact with receptors via their side chains. Phenylalanine and tryptophane can establish both hydrophobic interactions via the methylene side chain or the aromatic groups and π-π-interactions via the aromatic groups. Additionally, the indole group of the tryptophane can serve as a hydrogen bond donor via its NH group. Cyclohexyl alanine and norleucine can, in principle, establish hydrophobic interactions with biological receptors via their alkyl and/or cycloalkyl side chains. Not only the complete side chain of an amino acid, but also parts of the side chain can establish important interactions.

If a group or a unit, which is to mimic or imitate the biological binding characteristics of an amino acid or shall exhibit this characteristic, is capable of establishing at least one of the above-mentioned interactions of the respective amino acid, then this group or unit can mimic its biological binding characteristics.

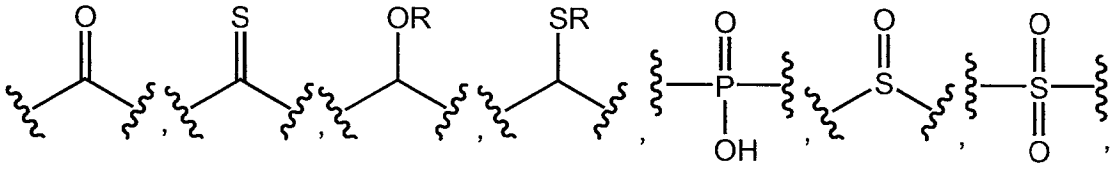
As used herein in connection with the definition of the groups, the term "and respective derivatives thereof" refers to the fact that all derivatives of the individual compounds, groups of compounds, parts of molecules, radicals or chemical groups as recited in the respective group, can each be present as derivatives.

As used herein the term "individually and independently" refers to the fact that the two or more substituents mentioned can be designed as described in the respective paragraph. The wording "individually and independently" shall only avoid unnecessary repetitions and discloses that any of the mentioned substituents can exhibit the described arrangement, whereby the arrangement

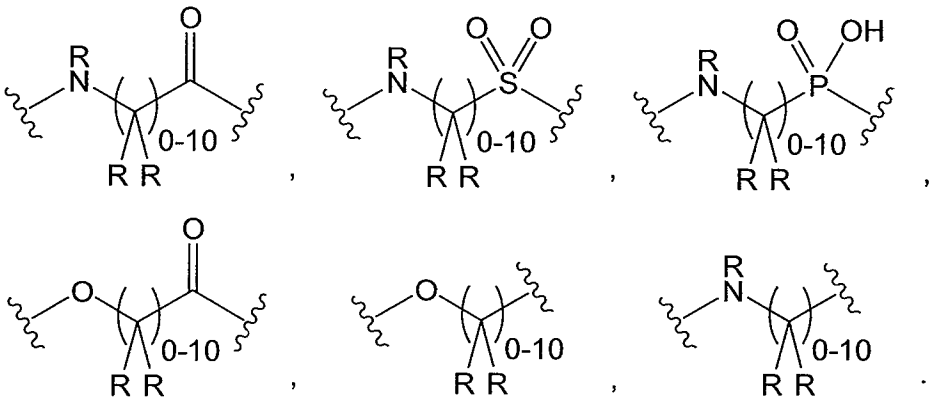
for each substituent is made individually or is individually present and is not affected by the selection of one or several of the other substituents.

It is generally within the scope of the present invention that the substituents described for the individual compounds according to the invention, in particular for the generic structures, are also applicable to all of the generic formulas with the corresponding substituents, if not indicated to the contrary.

Spacers as used herein, are in preferred embodiments organic radicals having a molecular weight of approximately 1-300, which allow a covalent linkage between different chemical groups if not indicated to the contrary for the individual case. Examples are simple groups like



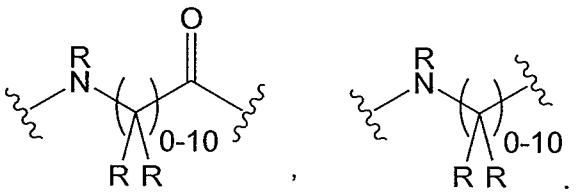
or more complex units like



wherein R is, for each substitution, individually and independently a residue with a molecular weight of approximately 1-300. Preferably, R is a radical selected from the group comprising H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkylalkyl, substituted cycloalkylalkyl, heterocyclyl, substituted heterocyclyl, heterocyclylalkyl, substituted heterocyclylalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroaryl alkyl, substituted heteroarylalkyl, acyl, substituted acyl, alkoxyalkyl, substituted alkoxyalkyl, aryloxyalkyl, substituted aryloxyalkyl, sulfhydrylalkyl, substituted

sulfhydrylalkyl, hydroxyalkyl, substituted hydroxyalkyl, carboxyalkyl, substituted carboxyalkyl, carboxamidoalkyl, substituted carboxamidoalkyl, carboxyhydrazinoalkyl, ureidoalkyl, aminoalkyl, substituted aminoalkyl, guanidinoalkyl and substituted guanidinoalkyl.

Spacers are preferably selected from the group comprising



wherein R is preferably a radical selected from the group comprising H, alkyl, substituted alkyl, arylalkyl, substituted arylalkyl, heteroarylalkyl and substituted heteroarylalkyl.

Peptides carrying a positive net charge, can cause a histamine release (Jasani et al. 1979 Biochemical Journal 181: 623-632). In particular subcutaneous administration and/or implantation of subcutaneous depots is not possible with such compounds. In case of orally administered drugs absorption of the drugs is particularly important. The absorption of charged molecules is usually inferior to the one of uncharged molecules under otherwise identical conditions (Veber et al. 2002 Journal of Medicinal Chemistry 45: 2615-2623). Due to the missing net charge of the compounds according to the present invention they are particularly suitable for use as oral drugs.

The inventions according to the present invention can be used for the manufacture of medicaments, in particular for the manifacture of medicaments for the prevention and/or treatment of immuno inflammatory diseases. In particular the following diseases belong to the group of immuno inflammatory diseases: autoimmune diseases, rheumatoid arthritis, systemic lupus erythematodes, reperfusion injury, myocardial infarction, stroke, multiple sclerosis, psoriasis, dialysis, septic shock, asthma, vasculitis, dermatomyositis, pemphigus, myasthenia grave, burns, organ rejection, acute respiratory insufficiency, intestinal reperfusion injury, and acute injuries of the central nervous system. All these diseases and/or clinical characteristics are mainly derived from the group of immuno inflammatory and inflammatory diseases, respectively, whereby the inflammatory response of these diseases may be either the cause or a secondary reaction thereof.

The present invention is also related to formulations, in particular pharmaceutical formulations, which comprise at least one of the compounds according to the invention. Frequently pharmaceutically active compounds are combined with other pharmaceutically acceptable ingredients, in order to ensure an improved efficacy like improved transport, shelf-life, release behavior over time and the like. A variety of such appropriate formulations are known to the one skilled in the art. Ingredients of such formulations are, among others, inert diluents, calcium carbonate, sodium carbonate, lactose, calcium phosphate, sodium phosphate, starch, alginate, gelatine, magnesium stearate and talcum. Certain ingredients can be added in order to allow for a retarded release of the pharmaceutically active active compounds. Respective examples are glycerol monostearate and glycerol distearate. For oral application in particular hard gelatine capsules are used, whereby the pharmaceutically active ingredient is admixed with calcium carbonate, calcium phosphate or kaolin. For soft gelatine capsules the pharmaceutically active compounds are admixed, e.g., with oils (peanut oil, liquid paraffin, olive oil). For the application in aqueous solutions the pharmaceutically active ingredients can be admixed in particular with the following components: carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, lecithin, polymer products of alkylene oxides and fatty acids as for example polyoxyethylenestearate, heptadecaethyleneoxycetanol, polyoxyethylenesorbitol monooleate and polyoxyethylenesorbitane monooleate. For the purpose of preservation different additives may be used. Respective examples are ethyl or n-propyl-p-hydroxybenzoate.

Certain formulations are used in order to allow for particular routes of administration. Examples of routes of administration of compounds according to the present invention are oral, subcutaneous, intravenous, topical, intramuscular, rectal and inhalativ administration. The compounds according to the present invention can be present as pharmaceutical acceptable salts.

Examples

Example 1: Material and methods

The materials and methods as well as general procedures described in the following were used in the following further examples:

Solvents:

All solvents were used in the specified quality without further purification.

Acetonitrile (gradient grade, J.T. Baker); dichloromethane (for synthesis, Merck Eurolab); diethylether (for synthesis, Merck Eurolab); *N,N*-dimethylformamide (LAB, Merck Eurolab); dioxane (for synthesis, Aldrich); methanol (for synthesis, Merck Eurolab).

Water was demineralised using a demineralization system (Milli-Q Plus, Millipore)

Reagents:

The used reagents were purchased from Advanced ChemTech (Bamberg, Germany), Sigma-Aldrich-Fluka (Deisenhofen, Germany), Bachem (Heidelberg, Germany), J.T. Baker (Phillipsburg, USA), Lancaster (Mühlheim/Main, Germany), Merck Eurolab (Darmstadt, Germany), Neosystem (Strassburg, France), Novabiochem (Bad Soden, Germany, from 2003 Merck Biosciences, Darmstadt, Germany) and Acros (Geel, Belgium, distributor Fisher Scientific GmbH, Schwerte, Germany), Peptech (Cambridge, MA, USA), Synthetech (Albany, OR, USA), Pharmacore (High Point, NC, USA), Anaspec (San Jose, CA, USA) and used in the specified quality without further purification.

Unnatural amino acids or carboxylic acids for N-terminal modification which were not commercially available, were prepared according to standard protocols. For example, Fmoc-cis-Hyp-OH was prepared by reacting h-cis-Hyp-OH with Fmoc OSu [Paquet et al. 1982 Canadian Journal of Chemistry 60: 976-980A]. Fmoc-Phe(4-STrt-amidino)-OH was synthesized according to a known protocol [Pearson et al. 1996 Journal of Medicinal Chemistry 39:1372-1382]. Side

chain modified cysteine derivatives were prepared by alkylation of Fmoc cystein-OH with alkyl halides.

If not indicated differently, concentrations are given as percent by volume.

RP-HPLC-MS analyses:

For analytic chromatography a Hewlett Packard series 1100 system (degasser G1322A, quaternary pump G1311A, automatic sample loader G1313A, column heater G 1316A, variable UV detector G1314A) was used together with an ESI-MS (Finnigan LCQ ion trap mass spectrometer). The system was controlled by "navigator ver. 1,1 sp1" software (Finnigan). Helium was used as impact gas in the ion trap. For separation a RP-18-column (Vydac 218 TP5215, 2.1 x 150 mm, 5 µm, C18, 300 A with a pre-column (Merck)) was used at 30°C and a flow of 0.3 ml/min using a linear gradient for all chromatograms (5-95 % B within 25 min, linear, whereby A: 0.05 % TFA in water and B: 0.05 % TFA in CH_3CN). UV detection was at λ = 220 nm. Retention times (R_t) are indicated in the decimal system (e.g. 1.9 min = 1 min 54 s) and are referring to detection in the mass spectrometer. The dead time between injection and UV detection (HPLC) was 1.65 min, and between UV detection and mass detection 0.21 min. The accuracy of the mass spectrometer was approx. ± 0.2 amu.

Analyses by means of HPLC/MS were performed by injection of 5 µl, using a linear gradient from 95:5 to 5:95 in 9.5 min (A: 0.05 % TFA in water and B: 0.05 % TFA in acetonitrile), RP columns were from the company Phenomenex, Type Luna (C-18), 3µm, 50 x 2.00 mm, flow 0.3 ml, HPLC at room temperature; mass spectrometer: ThermoFinnigan Surveyor with PDA detector (210 - 350 nm), MS; Advantage and/or LCQ Classic (both iontrap), ESI ionization, helium served as impact gas in the ion trap. Excalibur vers. 1.3 and 1.2, respectively, was used as software. Retention times (R_t) are indicated in the decimal system (e.g. 1.9 min = 1 min 54 s).

Preparative HPLC:

Preparative HPLC separations were done using Vydac R18-RP columns with gradients of the following solvents: 0.05 % TFA in H_2O and B: 0.05 % TFA in CH_3CN

Table 1: Abbreviations:

Fig.	Figure
AAV	General procedure
Ac	Acetyl
Acm	Acetamidomethyl
Ac	Acetyl
d	Doublet
DCM	Dichloromethane
DIC	Diisopropylcarbodiimide
DIPEA	N,N-Diisopropylethylamine
DMF	*N,N*-Dimethylformamide
DMEM	Dulbecco's Modified Eagle Medium
DMSO	Dimethylsulfoxide
eq.	Equivalent(s)
Fmoc	9-Fluorenylmethyloxycarbonyl
h	Hour(s)
HATU	O-(7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium-Hexafluorophosphate
HBTU	*O*-(Benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-Hexafluorophosphate
HEPES	N-2-2-Hydroxyethyl-1-piperazine-N´-2-ethanesulfonic acid
HOBt	1-Hydroxybenzotriazole
HPLC	High-pressure liquid chromatography
m	Multiplet
Me	Methyl
min	Minute(s)
ml	Milliliter
NMI	*N*-Methylimidazole
NMP	*N*-Methylpyrrolidone
NMR	Nuclear magnetic resonance
s	Singlet
^{t}Bu	tert-Butyl
THF	Tetrahydrofuran
TFA	Trifluoroacetic acid

Table 2: For proteinogenic amino acids the 3-letter codes were used:

3-letter code	Amino acids	3-letter code	Amino acids
Ala	Alanine	Met	Methionine
Cys	Cysteine	Asn	Asparagine
Asp	Aspartic acid	Pro	Proline
Glu	Glutamic acid	Gln	Glutamine
Phe	Phenylalanine	Arg	Arginine
Gly	Glycine	Ser	Serine
His	Histidine	Thr	Threonine
Ile	Isoleucine	Val	Valine
Lys	Lysine	Trp	Tryptophane
Leu	Leucine	Tyr	Tyrosine

Table 3: For non-proteinogenic amino acids a 3-letter code was used where the first letter indicates the stereochemistry of the C-alpha-atom. A capital first letter stands for the L-form, a lower case first letter stands for the D-form of the correspondent amino acid.

1Ni	1-Naphthylalanine
2Ni	2-Naphthylalanine
3PP	3-Phenylpropionyl
Aoa	Aminooxyacetic acid
Aoc	1-Aza-bicyclo-[3.3.0]-octan-2-carboxylic acid
Aze	Azetidine-2-carboxylic acid
Bta	Benzothienylalanine
Cha	beta-cyclohexylalanine
Chg	Cyclohexylglycine
Dab	γ-diaminobutyric acid
Cit	Citrullin
Eaf	Allylglycine
Eag	2-Propargylglycine

Eap	Phe(4-tBu)
Eay	4-Phenyl-pyrrolidine-2-carboxylic acid
Ebd	Cys(Et)
Ebo	Cys(4-picolyl)
Ebu	Cys(3-picolyl)
Ebw	3,3-Diphenylalanine
Eby	(S)-3-Amino-3-phenylpropanic acid
Ecf	Cys(O-3-picolyl)
Ecg	Cys(2-picolyl)
Ecp	His(tau-4-Methoxybenzyl)
Ecr	His(tau-methyl)
Edn	Cys(CH_2-CH_2-4-Pyridyl)
Eec	Cys(1-Methylene-1H-benzotriazole)
Eew	Arg(NO_2)
Guf	Phe(4-guanidine)
Har	Homo-Arginine
Hch	Homo-Cyclohexylalanine
Hci	Homo-Citrulline
Hle	Homo-Leucin
Hyp	Hydroxyprolin
Hyp	Hydroxyproline
Mpa	3-(3-Pyridyl)-alanine
Mcf	Phe(3-Cl)
Mpa	3-(3-Pyridyl)-alanine
Nle	Norleucine
Nva	Norvaline
Oic	Octahydroindole-2-carboxylic acid
Omf	Phe(2-Me)
Orn	Ornithine
Paf	Phe(4-NH_2)
Pcf	Phe(4-Cl)
Pff	Phe(4-F)
Phg	Phenylglycine

Pip	Pipecolinic acid
Pmf	Phe(4-Me)
Ppa	3-(4-Pyridyl)-alanine
Thi	2-Thienylalanine
Tic	1,2,3,4-Tetrahydroisochinoline-3-carboxylic acid
Tiq	Tetrahydroisochinoline-1-carbonxylic acid
XX1	2-Amino-3-(4-piperidinyl)propionic acid
XX2	4-Guanidyl-piperidinyl-alanine

The activity of the compounds was described in a simplified manner based upon the following conventions:

$IC_{50} < 5$ nM:	A
5 nM $< IC_{50} \leq 10$ nM:	B
10 nM $< IC_{50} \leq 20$ nM:	C
20 nM $< IC_{50} \leq 50$ nM:	D
50 nM $< IC_{50} \leq 200$ nM:	E
200 nM $< IC_{50} \leq 2000$ nM:	F
2000 nM $< IC_{50}$	G

General procedure (AAV) 1: Synthesis of linear peptides

Linear peptides were synthesized using the Fmoc-^{t}Bu-strategy in batch-mode. The synthesis was done either manually in polypropylene syringes with a frit or via an automatic synthesizer (Syro from Multisyntech, Witten or Sophas from Zinsser, Frankfurt).

For the preparation of peptides carrying a C-terminal carboxylic acid, the C-terminal amino acid was either attached to a tritylchloride resin (app. 200 mg resin; loading of reactive groups about 1.5 mmol/g; coupling with 0.8 eq. Fmoc-amino acid and 3.0 eq. DIPEA in CH_2Cl_2 for 2 h; obtained loading of the amino acid about 0,2-0,4 mmol/g) or to Wang resin (200-500 mg resin; loading of reactive groups about 0.6 mmol/g; coupling by reacting 4 eq. Fmoc-amino acid, 4 eq. DIC and 3 eq. NMI in DMF for 3 h; loading of the amino acid about 0.2-0.6 mmol/g).

For the preparation of peptides carrying a C-terminal carboxylic amide, the first amino acid was attached to the resin via Fmoc deprotection from the Fmoc-Rink amide resin (about 200 mg resin; Fmoc deprotection with 20 % piperidine in DMF for 20 min) and subsequent coupling of the Fmoc amino acid (reaction with 5 eq. Fmoc amino acid; 5 eq. HBTU and 15 eq. DIPEA in DMF for 30-60 min repeated once or more times).

After the coupling of the first amino acid, the synthesis of the desired peptide was done via a repeated sequence of events, as necessary, consisting of Fmoc deprotection and coupling of each of the required Fmoc amino acid or carboxylic acids. For the Fmoc deprotection the resin was reacted with 20 % piperidine in DMF for 20 min. The coupling was carried out via single or multiple reaction with 5 eq. of the amino acid, 5 eq. HBTU and 15 eq. DIPEA in DMF for 30-60 min. For the introduction of the N-terminal acetyl group, the N-terminal free peptide, bound to the resin, was reacted with a solution of 10 % acetic acid anhydride and 20 % DIPEA in DMF for 20 min.

For the cleavage of the peptide from the resin and removal of the side chain protecting groups, a mixture of 95 % TFA, 2,5 % H_2O, 2,5 %TIPS or a similar solution was added. Finally, TFA was removed using a rotary evaporator or the obtained peptide was precipitated by adding methyl-^{t}butyl-ether at 0°C and isolated by centrifugation or pouring off the supernatant. For the transformation of the optionally obtained TFA-salts into the correspondent HCl salts, the peptide was solubilized in a mixture of 2 N HCl and MeCN and lyophilized.

Peptides with C-terminal carboxylic amides were directly purified via HPLC. Peptides carrying C-terminal carboxylic acids, however, were cyclized as raw product in accordance with AAV2.

General procedure (AAV) 2: Cyclization of peptides having a C-terminal carboxylic acid

For cyclization about 80 mg of the linear peptide synthesized in accordance with AAV1, were solubilized in 5 ml DMF and 5 ml CH_2Cl_2. Subsequently, the pH was set to a value of approx. 8 with N-ethylmorpholine and 1 eq. HOBt was added together with 10 eq. DIC. After 2-16 h of stirring at room temperature the solvent removed using a rotary evaporator and the raw product purified via HPLC.

General procedure (AAV) 3: Reductive alkylation of resin-bound peptides having a free N-terminus

Linear peptides, synthesized in accordance with AAV1, with a free N-terminus were incubated, prior to cleavage from the resin, with 10 eq. of the corresponding aldehyde in 5 % acetic acid and 5 % trimethylorthoformiate in THF. After approx. 4 h the obtained imine was reduced overnight with 5 eq. sodium cyanoborhydride.

After cleavage from the resin of the peptide completely synthesized in accordance with AAV1 the obtained raw product could be cyclized in accordance with AAV2. Usually an undesired cyclization to the N-terminal secondary amine occurred apart from the desired cyclization. This byproduct could easily be removed by HPLC.

Example 2: Synthesis of Ac-Phe-[Orn-Pro-cha-Trp-Phe] (1)

After linear peptide synthesis in accordance with AAV 1, cyclization in accordance with AAV 2, and subsequent purification via HPLC, 50.9 mg of the desired product Ac-Phe-[Orn-Pro-cha-Trp-Phe] were obtained as white solid.

MS (ESI): m/z = 888.3 $[(M+H)^+]$.

Example 3: Synthesis of Ac-Phe-[Orn-Hyp-cha-Trp-Phe] (2)

The linear peptide Ac-Phe-Orn-Hyp-cha-Trp-Phe-OH was obtained by linear peptide synthesis in accordance with AAV 1 and cyclized in accordance with AAV 2. Due to the higher nucleophilicity of amines compared to alcohols, no byproduct together with the desired cyclized product was obtained through coupling of the free Hyp-OH group with the C-terminal carboxylic acid. Purification of the obtained raw product via HPLC yielded 26.9 mg of the desired white solid Ac-Phe-[Orn-Hyp-cha-Trp-Phe] (**2**).

MS (ESI): m/z = 903.5 $[(M+H)^+]$.

Example 4: Synthesis of Ph-CH_2-[Orn-Pro-cha-Trp-Nle] (56)

The resin-bound peptide H-Orn-Pro-cha-Trp-Nle-trityl-resin was prepared by linear peptide synthesis in accordance with AAV1 and subjected to reductive alkylation using benzaldehyde. The cyclization in accordance with AAV 2, and subsequent purification via HPLC yielded 0.9 mg of the desired product **56** as white solid.

MS (ESI): m/z = 753.4 $[(M+H)^+]$.

Example 5: Synthesis of $HOCH_2(CHOH)_4$-C=N-O-CH_2-CO-Phe-[Orn-Pro-cha-Trp-Nle] (3)

The linear peptide H-Aoa-Phe-Orn-Pro-cha-Trp-Nle-OH was prepared in accordance with AAV 1, solubilized in 24 ml 1:1 MeCN/sodium acetate buffer (0.2 M, pH = 4) and incubated with 58 mg (10 eq.) D-glucose. After stirring for 5 days, 2.4 ml acetone were added for quenching the unreacted aminooxyacetic acid-peptide, and after 5 min the solvent was evaporated under vacuum. The obtained raw product was purified via HPLC and subsequently cyclized in accordance with AAV 2. The purification of the raw product via HPLC yielded 1.9 mg of the desired white solid **3**.

MS (ESI): m/z = 1046.5 [$(M+H)^+$].

Example 6: Synthesis of 2-Acetamido-1-Methyl-Glucuronyl-Phe-[Orn-Pro-cha-Trp-Nle] (4)

The resin-bound peptide H-Phe-Orn-Pro-cha-Trp-Nle-trityl-resin was prepared by linear peptide synthesis in accordance with AAV 1, reacted with 39.8 mg (2.0 eq.) 2-acetamido-1-methyl-glucuronic acid (Schämann et al. 2003 European Journal of Organic Chemistry: 351-358), 60.8 mg (2.0 eq.) HATU and 105.7 µl (10 eq.) 2,4,6-collidine in 1.6 ml DMF. After stirring for 1.5 h the resin was washed with DMF (5x), MeOH (5x) und CH_2Cl_2 (3x) and the peptide was cleaved from the resin using 95 % TFA, 2.5% H_2O and 2.5 % TIPS. Cyclization in accordance with AAV 2, and HPLC purification yielded 29,0 mg of the desired product **4** as white solid.

MS (ESI): m/z = 1043.0 [$(M+H)^+$].

Example 7: Synthesis of Ac-Phe-[Orn-Hyp($COCH_2OCH_2CH2OCH_2CH_2OCH_3$)-cha-Trp-Nle] (5)

The linear peptide Ac-Phe-Orn-Hyp-cha-Trp-Nle-OH was prepared in accordance with AAV 1, was cyclized in accordance with AAV 2 and the resulting cyclic peptide Ac-Phe-[Orn-Hyp-cha-Trp-Nle] was purified via HPLC. 35.4 µl (40 eq.) 2-(2-(2-Methoxyethoxy)ethoxy)acetic acid were reacted with 50.3 µl (120 eq.) thionyl chloride for 15 min at 40°C. After removal of the solvent under vacuum, 78.8 ml (80 eq.) DIPEA, 1 ml CH_2Cl_2 and 5.0 mg of the compound Ac-Phe-[Orn-Hyp-cha-Trp-Nle] were added. Stirring was continued for 3 days at room temperature and purification was done via HPLC. This yielded 1.6 mg of the desired white solid **5**.

MS (ESI): m/z = 1029.6 [$(M+H)^+$].

Example 8: Synthesis of Ac-Phe-[Orn-Hyp(CONH-$CH_2CH(OH)$-CH_2OH)-cha-Trp-Nle] (6)

The linear peptide Ac-Phe-Orn-Hyp-cha-Trp-Nle-OH was synthesized in accordance with AAV 1, cyclized in accordance with AAV 2, and the resulting cyclic peptide Ac-Phe-[Orn-Hyp-cha-Trp-Nle] was purified via HPLC. Subsequently, 5.0 mg of the peptide were reacted with 26.1 mg 4-isocyanatomethyl-2,2-dimethyl-[1,3]dioxolane and 1.88 µl (2.0 eq.) DIPEA in 0.3 ml MeCN. After stirring for 3 days at 40°C, the solvent was removed by a rotary evaporator and the obtained raw product was purified via HPLC. 0.22 mg of the desired white solid **6** were obtained.

MS (ESI): m/z = 986.5 $[(M+H)^+]$.

Example 9: Synthesis of Ac-Phe-[Orn-Pro-cha-Trp-Arg(CH_2CH_2)] (7)

The linear peptide Ac-Phe-Orn-Pro-cha-Trp-Orn-OH was synthesized in accordance with AAV 1, cyclized in accordance with AAV 2, and the resulting cyclic peptide Ac-Phe-[Orn-Pro-cha-Trp-Orn] was purified via HPLC. Subsequently, 2.6 mg of the peptide were reacted with 22.6 mg (30 eq.) 2-(methylmercapto)-2-imidazoline-hydroiodide and 29.7 µl (60 eq.) DIPEA in 260 µl MeOH. After stirring for 2 days at 50°C, the solvent was removed by a rotary evaporator and the resulting raw product was purified via HPLC. 0.86 mg of the desired white solid **7** were obtained.

MS (ESI): m/z = 922.8 $[(M+H)^+]$.

Example 10: Synthesis of Ph-CH_2-CH_2-CO-[Orn-Pro-cha-Trp-Nle] (41)

The peptide Ph-CH_2-CH_2-CO-Orn-Pro-cha-Trp-Nle-OH was prepared by linear peptide synthesis in accordance with AAV1, whereby 3-phenylpropionic acid was used as N-terminal carboxylic acid. Cyclization was performed in accordance with AAV 2 and the raw product was purified via HPLC. 3.13 mg of the desired white solid **41** were obtained.

MS (ESI): m/z = 796.5 [$(M+H)^+$].

Example 11: Determination of the IC_{50} value in an enzyme release assay

The assay procedure is described in Köhl (Köhl 1997 The Anaphylatoxins. In: Dodds, A.W., Sim, R.B. (Eds.), Complement: A Practical Approach. Oxford, pp. 135-163). Basophilic leukemia cells from rats (RBL), which express the human C5aR (CD88), were cultivated in DMEM with 10 % fetal bovine serum, 100 U/ml penicillin, 100 µg/ml streptomycin and 2 mM glutamine (all components of the medium from Biochrome, Berlin) until confluence at 37°C and 10 % CO_2. The following specifications all refer to a cell culture flask having a surface of 75 cm^2. Spent medium was decanted from cells. Cells were washed with 10 ml PBS (Dulbecco's PBS, Biochrome) and subsequently overlayed with 3 ml Cell Dissociation Solution (CDS, Sigma). Cells were incubated for 1 min at room temperature. Subsequently, CDS was removed and the cells were further incubated 10-15 min at 37°C for detachment. In the assay, 20 µl of the solution containing the compound to be tested were used. This assay solution must not contain more than 2.8 % DMSO. For the dilution process, the compounds were diluted in 1/3 or 1/2 steps. To 20 µl compound solution 75 µl of the RBL-cells were added which were treated as follows: after detachment the cells were vigorously tapped off and taken up in 10 ml HAG-CM (20 mM HEPES; 125 mM NaCl, 5 mM KCl, 1 mM $CaCl_2$, 1 mM $MgCl_2$, 0,5 mM Glucose, 0,25 % BSA. HEPES-preparation: 2.3 g/l HEPES-salt + 2.66 g/l HEPES acid) at 37° C. Cells were counted and centrifuged (200xg, 10 min). The cell pellet was resuspended in preheated HAG-CM (i.e. Hepes-buffered solution of NaCl and glucose with calcium and magnesium), and cell density was adjusted to $2x10^6$ cells/ml. The cells were incubated at 37°C for 5 min. 27 µl of a cytochalasin B-solution were added per ml cell suspension (100 µg/ml in DMSO, Sigma). The cells were incubated for further 3 min at 37°C. 75 µl of the cell suspension were added to 20 µl of the solution containing the compound to be tested, leading to a volume of 95 µl per well. After incubation of the cells for 10 min at 37°C 10 µl hrC5a (10.5 nM in HAG-CM, Sigma) are added per well. Subsequently, the cells are incubated for 5 min at 37°C. Thereafter, the plates are put on ice and centrifugated at 1200 xg and 4° C for 3 min. 75 µl of the supernatant are added to 100 µl substrate solutions (2.7 mg/ml p-nitrophenyl-N-acetyl-β-D-glucosaminide (Sigma) in 42.5 mM Na-acetate pH 4.5). The plate further is incubated for 1 h at 37°C. 75 µl 0.4 M glycine pH 10.4 are added per well. The plate can subsequently be measured in a reader at 405 nm. The IC_{50}-value is determined by solving the four parameter equation: $y=((A-D)/(1+(x/C)^B))+D$.

The results of the IC_{50}-value determination are shown in table 4.

Table 4: Data for antagonistic activity of selected compounds acording to the present invention.

No.	Compound	(M+H)+ in MS [amu]	activity (group)
1	Ac-Phe-[Orn-Pro-cha-Trp-Phe]	888.3	D
2	Ac-Phe-[Orn-Hyp-cha-Trp-Phe]	903.5	D
3	HOCH2(CHOH)4-C=N-O-CH2-CO-Phe-[Orn-Pro-cha-Trp-Nle]	1046.5	E
4	X-Phe-[Orn-Pro-cha -Trp-Nle]; X = 2-Acetamido-1-Methyl-Glucuronyl	1043.0	D
5	Ac-Phe-[Orn-Hyp(COCH2OCH2CH2OCH2CH2OCH3)-cha-Trp-Nle]	1029.6	E
6	Ac-Phe-[Orn-Hyp(CONH-CH2CH(OH)-CH2OH)-cha-Trp-Nle]	986.5	E
7	Ac-Phe-[Orn-Pro-cha-Trp-Arg(CH2CH2)]	922.8	F
8	Ac-Phe-[Orn-Pro-cha-Trp-Har]	910.7	F
9	Ac-Phe-[Orn-Pro-cha-Trp-Guf]	944.6	F
10	Ac-Phe-[Orn-Pro-cha-Trp-Cit]	897.5	F
11	Ac-Phe-[Orn-Pro-cha-Trp-Eew]	941.5	F
12	Ac-Phe-[Orn-Pro-cha-Trp-arg]	896.7	F
13	Ac-Phe-[Orn-Pro-cha-Trp-Hci]	911.6	F
14	Ac-Phe-[Orn-Pro-cha-Trp-Paf]	902.7	D
15	Ac-Phe-[Orn-Pro-cha-Trp-Ebo]	934.6	F
16	Ac-Phe-[Orn-Pro-cha-Trp-Ecf]	950.6	F
17	Ac-Phe-[Orn-Pro-cha-Trp-Ebu]	934.7	F
18	Ac-Phe-[Orn-Pro-cha-Trp-Ecg]	934.6	F
19	Ac-Phe-[Orn-Pro-cha-Trp-Edn]	948.6	F
20	Ac-Phe-[Orn-Pro-cha-Trp-Ecr]	891.7	E

21	Ac-Phe-[Orn-Pro-cha-Trp-Phe(4-Amidin)]	929.7	F
22	Ac-Phe-[Orn-Pro-cha-Trp-Lys]	868.6	G
23	Ac-Phe-[Orn-Pro-cha-Trp-Ppa]	888.6	E
24	Ac-Phe-[Orn-Pro-cha-Trp-Arg(Me2)]	924.7	E
25	Ac-Phe-[Orn-Pro-cha-Trp-Dab]	840.4	E
26	Ac-Phe-[Orn-Pro-cha-Trp-Ecp]	997.7	F
27	Ac-Phe-[Orn-Pro-cha-Trp-XX1]	894.6	G
28	Ac-Phe-[Orn-Pro-cha-Trp-Nle]	852.6	D
29	Ac-Phe-[Orn-Pro-cha-Trp-Met]	871.6	E
30	Ac-Phe-[Orn-Pro-cha-Trp-XX2]	936.5	G
31	Ac-Phe-[Orn-Pro-cha-Trp-Nva]	839.5	C
32	Ac-Phe-[Orn-Pro-cha-Trp-Hle]	867.5	D
33	Ac-Phe-[Orn-Pro-cha-Trp-Eaf]	837.5	B
34	Ac-Phe-[Orn-Pro-cha-Trp-Ebd]	871.5	D
35	Ac-Phe-[Orn-Pro-cha-Trp-Eag]	835.5	B
36	Ac-Phe-[Orn-Pro-cha-Trp-Pmf]	901.6	D
37	Ac-Phe-[Orn-Pro-cha-Trp-2Ni]	937.5	E
38	Ac-Phe-[Orn-Pro-cha-Trp-Thi]	893.5	D
39	Ac-Phe-[Orn-Pro-cha-Trp-Ala]	811.7	G
40	Ac-Phe-[Orn-Pro-cha-Trp-Arg]	896.6	C
41	Ph-CH2-CH2-CO-[Orn-Pro-cha-Trp-Nle]	796.5	C
42	H-Phe-[Orn-Pro-cha-Trp-Nle]	811.5	C
43	Ac-Lys-Phe-[Orn-Pro-cha-Trp-Nle]	1015.7	D
44	H-Phe-[Orn-Ser-cha-Trp-Nle]	843.5	D
45	Ac-Ala-[Orn-Pro-cha-Trp-Arg]	820.6	G
46	Ac-Phe-[Orn-NMeAla-cha-Trp-Arg]	884.8	D
47	Ac-Phe-[Orn-Pro-ala-Trp-Arg]	814.8	G
48	Ac-Phe-[Orn-Pro-cha-Ala-Arg]	781.8	G
49	Ac-Phe-[Orn-Pro-cha-Trp-Ala]	811.7	G
50	Ac-Phe-Orn-Pro-cha-Trp-Arg-NH_2	913,3	E
51	Ac-Phe-Orn-Pro-cha-Trp-Phe-NH_2	904,5	D
52	Ac-Phe-Orn-Aze-cha-Bta-Phe-NH_2	907,5	C

53	Ac-Phe-Orn-Pro-cha-Bta-2Ni-NH_2	954,4	D
54	Ac-Phe-Orn-Pro-cha-Bta-Cha-NH_2	910,5	E
55	Ac-Phe-Orn-Pip-cha-Trp-Phe-NH_2	941,3	D
56	Ph-CH2-[Orn-Pro-cha-Trp-Nle]	753.4	D
57	Ph-CH2-[Orn-Pro-cha-Trp-Phe]	787.5	D
58	Ac-Phe-[Orn-Pro-cha-Trp-1Ni]	937.7	D
59	Ph-CH(OH)-CH_2-CO-[Orn-Pro-cha-Trp-Nle]	812,4	D
60	Ac-Phe-Lys-Ala-Cha-Ala-Leu-ala-Tyr-OH	978,9	G
61	Ac-Phe-Orn-Pro-cha-Trp-Phe-NH_2	904,9	D
62	Ac-Phe-Orn-Pro-cha-Bta-Phe-NH_2	921,8	D
64	Ac-Phe-Orn-Pro-cha-Trp-2Ni-NH_2	954,9	D
65	Ac-Phe-Orn-Pro-cha-Trp-Cha-NH_2	911,1	E
66	Ac-Thi-Orn-Aze-cha-Bta-Phe-NH_2	913,5	C
67	Ac-Thi-Orn-Pip-cha-Bta-Phe-NH_2	941,3	D
68	Ac-Phe-Orn-Pro-cha-Trp-Eap-NH_2	960,9	F
69	Me_2-Phe-Orn-Pro-cha-Trp-Phe-NH_2	890,8	E
70	Ph_2-CH-CH_2-CO-Orn-Pro-cha-Trp-Phe-NH_2	923,7	F
71	Ac-Ebw-Orn-Pro-cha-Trp-Phe-NH_2	980,8	F
72	Ac-Phe-Orn-Pro-cha-Trp-NH-CH_2-CH_2-Ph	861,8	F
73	Ac-Phe-Orn-Aze-cha-Bta-NH-CH_2-CH_2-Ph	864,7	F
74	H-Phe-Orn-Pro-cha-Trp-Phe-NH_2	862,7	E
75	H-Me-Phe-Orn-Pro-cha-Trp-Phe-NH_2	876,7	E
76	Bu-NH-CO-Phe-Orn-Pro-cha-Trp-Phe-NH_2	961,8	F
77	Ac-Thi-Orn-Pro-cha-Trp-Phe-NH_2	910,7	E
78	Ac-Ebw-Orn-Pro-cha-Trp-Phe-NH_2	980,8	E
79	Ac-Phe-Orn-Ala-cha-Trp-Phe-NH_2	878,7	E
80	Ac-Phe-Orn-Pro-cha-Trp-Thi-NH_2	910,7	E
81	Ac-Phe-Orn-Aze-cha-Pcf-Phe-NH_2	885,7	F
82	Ac-Phe-Orn(Ac)-Pro-cha-Trp-Phe-NH_2	946,9	E
83	Ac-Phe-Orn-Aze-cha-Trp-Phe-NH_2	890,9	D
84	Ac-Phe-Trp-Pro-cha-Trp-Phe-NH_2	976,5	E
85	Ph-NH-CO-Phe-Orn-Pro-cha-Trp-Phe-NH_2	981,7	E

86	Bu-O-CO-Phe-Orn-Pro-cha-Trp-Phe-NH_2	963,2	F
87	Ac-Phe-Lys-Pro-cha-Trp-Phe-NH_2	918,4	E
88	Ac-Phe-Arg-Pro-cha-Trp-Phe-NH_2	946,4	D
89	Ac-Phe-Gln-Pro-cha-Trp-Phe-NH_2	918,4	F
90	Ac-Phe-Ser-Pro-cha-Trp-Phe-NH_2	877,3	F
91	Ac-Phe-Glu-Pro-cha-Trp-Phe-NH_2	919,3	F
92	Ac-Phe-Orn-Pip-cha-Trp-Phe-NH_2	919,8	E
93	Ac-Phe-Orn-Hyp-cha-Trp-Phe-NH_2	920,3	F
94	Ac-Phe-Orn-Pro-cha-Trp-1Ni-NH_2	934,5	D
95	Ac-Phe-Orn-Aze-cha-Bta-Phe-NH-Me	921,6	F
96	CH_3-SO_2-Phe-Orn-Aze-cha-Bta-Phe-NH_2	943,9	D
99	Ac-Phe-Orn-Aze-cha-Pff-Phe-NH_2	869,7	E
100	Ac-Phe-Orn-Aze-cha-Mcf-Phe-NH_2	885,7	E
101	Ac-Phe-Orn(Ac)-Aze-cha-Bta-Phe-NH_2	921,7	D
102	Ac-Ebw-Orn-Pro-cha-Trp-Phe-NH_2	980,8	E
103	Ac-Phe-Trp-Pro-cha-Trp-Phe-NH_2	876,5	E
104	Ac-Phe-Arg-Pro-cha-Trp-Phe-NH_2	946,4	E
105	Ac-Phe-Orn-Pip-cha-Trp-Phe-NH_2	919,8	E
106	3PP-Orn-Aze-cha-Bta-Phe-NH_2	850,8	E
107	Ac-Phe-Orn-Tic-cha-Trp-Phe-NH_2	966,3	E
108	Ac-Phe-Orn-Ser-cha-Trp-Phe-NH_2	894,5	D
109	Ac-Phe-Orn-Pro-chg-Trp-Phe-NH_2	890,4	E
110	Ac-Phe-Orn-Pro-hch-Trp-Phe-NH_2	918,5	D
111	Ac-Phe-Orn-Pro-cha-Trp-Phg-NH_2	890,4	F
112	Ac-Phe-Bta-Aze-cha-Bta-Phe-NH_2	996,6	D
113	Ac-Phe-Trp-Pro-cha-Bta-Phe-NH_2	993,7	E
115	Ac-Phe-Orn-Pip-cha-Trp-Phe-OH	919,4	F
116	Ac-Phe-Orn-Tic-cha-Trp-Phe-OH	967,7	F
117	Ac-Phe-Orn-Ser-cha-Trp-Phe-OH	895,7	F
118	Ac-Phe-Orn-Pro-chg-Trp-Phe-OH	891,8	F
119	Ac-Phe-Eec-Pro-cha-Bta-Phe-NH_2	1041,7	E
120	Ac-Phe-Nle-Pro-cha-Bta-Phe-NH_2	920,5	E

121	Ac-Phe-Har-Pro-cha-Bta-Phe-NH_2	978,0	D
122	Ac-Phe-Arg-Pro-cha-Bta-Phe-NH_2	964,0	D
123	Ac-Phe-Cys(Acm)-Pro-cha-Bta-Phe-NH_2	981,5	F
124	Ac-Phe-Mpa-Pro-cha-Bta-Phe-NH_2	955,7	E
125	Ac-Eby-Orn-Pro-cha-Bta-Phe-NH_2	921,7	D
126	Ac-Phg-Orn-Pro-cha-Bta-Phe-NH_2	907,8	E
127	Ac-Phe-Paf-Pro-cha-Bta-Phe-NH_2	969,6	F
128	H_2N-CO-Phe-Orn-Pro-cha-Bta-Phe-NH_2	922,8	D
129	Me-O-CO-Phe-Orn-Pro-cha-Bta-Phe-NH_2	937,8	E
130	(-CO-CH_2-NH-CO-)-Phe-Orn-Pro-cha-Bta-Phe-NH_2	962,9	E
132	Ac-Phe-Orn-Pro-hch-Trp-Phe-OH	919,8	E
133	(-CO-CH_2-CH_2-CO-)-Phe-Orn-Pro-cha-Bta-Phe-NH_2	961,9	F
134	^{t}Bu-CO-Phe-Orn-Pro-cha-Bta-Phe-NH_2	963,9	E
135	Ac-Lys-Phe-Orn-Aze-cha-Bta-Phe-NH_2	1036,0	C
136	Ac-Gly-Phe-Orn-Aze-cha-Bta-Phe-NH_2	965,0	D
137	Ac-Arg-Phe-Orn-Aze-cha-Bta-Phe-NH_2	1064,1	D
138	Ac-His-Phe-Orn-Aze-cha-Bta-Phe-NH_2	1045,0	E
139	Ac-Ser-Phe-Orn-Aze-cha-Bta-Phe-NH_2	995,0	E
140	Ac-Guf-Phe-Orn-Aze-cha-Bta-Phe-NH_2	1112,1	E
141	Ac-Dab-Phe-Orn-Aze-cha-Bta-Phe-NH_2	1008,0	E
142	FH_2C-CO-Phe-Orn-Pro-cha-Bta-Phe-NH_2	939,8	D
143	Ac-Phe-Orn(Et_2)-Pro-cha-Trp-Phe-NH_2	960,9	E
144	Ac-Phe-[Orn-Hyp-cha-Trp-Nle]	868,6	C
145	3PP-[Orn-Hyp-cha-Trp-Nle]	811,6	D
146	Ac-Phe-[Orn-Pro-cha-Trp-Tyr]	902,7	D
147	Ac-Phe-[Orn-Pro-omf-Trp-Nle]	860,6	C
148	Ac-Phe-N(^{n}Bu)-CH_2-CO-Pro-cha-Trp-Phe-NH_2	920,8	F
149	Ac-Phe-Orn-Pro-hle-Bta-Phe-NH_2	895,4	C
150	Ac-Phe-Arg(CH_2-CH_2)-Pro-cha-Bta-Phe-NH_2	990,1	B

Example 12: Determination of EC_{50} values in an enzyme release assay

The determination of the EC_{50} value was performed in a way similar to the procedure described in example 11, with the only exception that 30 µl of the compound to be tested were mixed with 75 µl of the cell suspension described in example 11. There was no preincubation or addition of C5a for stimulation of the enzyme release. The results for the tested compounds are shown in table 5.

Table 5: Data for agonistic activity of selected compounds according to the present invention

No.	Compound	EC_{50} (nM)
-	hrC5a	2,4
3	HOCH2(CHOH)4-C=N-O-CH2-CO-Phe[OP-dCha-W-Nle]	»1430
41	Ph-CH_2-CH_2-CO-[Orn-Pro-cha-Trp-Nle]	»1430
2	Ac-Phe-[Orn-Hyp-cha-Trp-Phe]	»1430
42	H-Phe-[Orn-Pro-cha-Trp-Nle]	»1430
1	Ac-Phe-[Orn-Pro-cha-Trp-Phe]	»1430
43	Ac-Lys-Phe-[OP-dCha-W-Nle]	»1430
28	H-Phe-[Orn-Pro-cha-Trp-Nle]	»1430
44	H-Phe-[Orn-Ser-cha-Trp-Nle]	»1430
33	Ac-Phe-[Orn-Pro-cha-Trp-Eaf]	»1430
61	Ac-Phe-Orn-Pro-cha-Trp-Phe-NH_2	>100000
62	Ac-Phe-Orn-Pro-cha-Bta-Phe-NH_2	>100000
71	Ac-Ebw-Orn-Pro-cha-Trp-Phe-NH_2	>100000
88	Ac-Phe-Arg-Pro-cha-Trp-Phe-NH_2	>100000
55	Ac-Phe-Orn-Pip-cha-Trp-Phe-NH_2	>100000
83	Ac-Phe-Orn-Aze-cha-Trp-Phe-NH_2	>100000
84	Ac-Phe-Trp-Pro-cha-Trp-Phe-NH_2	>100000
67	Ac-Thi-Orn-Pip-cha-Bta-Phe-NH_2	>100000

Example 13: Solubility Determination for selected C5aR-antagonists

The solubility of compounds was determined by the following procedure: 20 µl of a 10 mM stock solution (in DMSO) of the compound were diluted in 980 µl of the solvent to be tested. After incubation for 24 h at RT under shaking the samples are centrifuged at 11.000 rpm in an Eppendorf centrifuge. The supernatant is determined by photometry. The opiteal density of the sample and of a control in 60 % MeOH served as a measure for the solubility. Compounds that showed a similarly good solubility in the solvent to be tested as in the control were tested for their maximum solubility as follows. Therefor the compound was suspended at 10 mg/ml in the solvent systems of choice. The undissolved part was removed by centrifugation after 24 h. The UV-absorption of the supernatant was measured and compared to a respective reference value (60 % MeOH). The solubility of some of the compounds according to the invention is shown in table 6.

Table 6: Solubility of some representatives of the compounds according to the invention

No.	Compound	Solubility in 20 mM HEPES pH 7.4 (% of 200 µM)
1	**Ac-Phe-[Orn-Pro-cha-Trp-Phe]**	8
2	**Ac-Phe-[Orn-Hyp-cha-Trp-Phe]**	13
28	**Ac-Phe-[Orn-Pro-cha-Trp-Nle]**	22
42	**H-Phe-[Orn-Pro-cha-Trp-Phe]**	45
4	**X-Phe-[Orn-Pro-cha -Trp-Nle]; X = 2-Acetamido-1-Methyl-Glucuronyl**	84
40	**Ac-Phe-[Orn-Pro-cha-Trp-Arg]**	94
43	**Ac-Lys-Phe-[Orn-Pro-cha-Trp-Nle]**	93

Example 14: Development of a pharmacophor model underlying the antagonists

The exchange of argenine in compound **40** by alanine (**39**) outlines the importance of the side-chain in this position for the inhibitory activity if the peptide. The replacement of arginine by the positively charged amino acid lysine **22** surprisingly results in an increase of the IC_{50} value (from

20 nM to 8700 nM). This means that the positive charge alone is not responsible for the antagonistic activity. The introduction of 4-aminophenylalanine (Paf) **14** to the C-terminal position results in an IC_{50}-value of 30 nM. The amino-group in Paf has a similar distance to the Cα-atom compared to the amino group in lysine. The exchange of arginine in compound **40** with the uncharged and very hydrophobic phenylalanine results in compound **1**, which surprisingly shows an IC_{50}-value (23 nM) comparable to the one of compound **40**. This clearly shows that, surprisingly, not the positively charged side chain of Arg and Paf, respectively, is responsible for the critical interaction with C5aR, but the hydrophobic part of Paf, Phe and the aliphatic side chain of arginine, respectively. It is possible to replace the arginine by other, hydrophobic substitutions without a significant increase of the IC_{50}-value compared to compound **40**. Examples for these types of substitutions are shown, among others, in compounds **1**, **28**, **29**, **31**, **32**, **33**, **34**, **35**, **36**, **37**, **38**.

The exchange of further amino acids in **40** by Ala, N-Me-Ala, or d-Ala revealed that the side chains of the following amino acids are important for antagonistic activity: Phe, cha, Trp.

A pharmacophor model was developed based on the structure-activity relationship of these and additional peptides. The distances for the important residues (two hydrophobic and two aromatic groups) for activity are predicted by the following method:

The pharmacophor model was developed based on a 2 ns lasting molecular dynamic simulation (increment of 2 fs) of compound **28**. The simulation was performed using AMBER94-force field and an explicit Water-model (TIP3) under periodic frame work. The static analysis of the snapshots from the last nanosecond of the trajectory (1000 structures) gave the distances between the mass-centered pharmacophor groups (see below).

The starting structure for the molecular dynamic simulation was based on ensemble-dynamic calculations with seven cyclic peptides. The peptides were highly active (IC_{50} in the lower nanomolar range) and with structure-restricting properties when compared to each other.

Example 15: Measurement of the AB- permeability in a TC-7 based assay-system

The compounds to be tested are diluted to a concentration of 50 µM in HBSS-MES (5 mM, pH 6.5) from 10 mM stock solution in 100 % DMSO. ^{14}C-mannitol (approx. 4 µM) is added to the sample. Subsequently, the solution is centrifuged and the supernatant is added to the apical side of a TC-7 cell culture (passage 15, in a 24 well transwell plate) to a final DMSO-concentration of 1 %. HBSS-HEPES (5 mM, pH 7.4) is placed at the basolatheral side. Subsequently, the cells were incubated for 120 min at 37°C. The integrity of the TC-7 cell-layer was tested by the added mannitol (P_{app} <2.5 10^{-6} cm/s). The permeability P_{app} [cm/s] is derived from the equation $(V_R x C_{R120})/(\Delta t x A x (C_{D,mid}-C_{R,mid}))$, whereby V_R is the volume of the receiver chamber, C_{R120} is the concentration of the test compound in the receiver camber after 120 min, Δt is the incubation time, A is the area of the TC-7 cell-layer, $C_{D,mid}$ is the midpoint concentration of the test compound in the donor chamber and $C_{R,mid}$ is the concentration of the test compound in the receiver chamber.

Compound	AB-permeability [cm/s]
Ac-Phe[Orn-Pro-cha-Trp-Arg]	0.52
Ac-Phe[Orn-Hyp-cha-Trp-Phe]	14.25

Example 16: Synthesis of Ac-Phe-Orn-Pro-cha-Trp-Phe-NH_2 (51)

The peptide was prepared by linear peptide synthesis in accordance with AAV 1. Subsequent, purification by HPLC yielded 10.0 mg of the desired product **51**as a white solid.

MS (ESI): m/z = 904.5 $[(M+H)^+]$.

Example 17: Synthesis of Ac-Phe-Orn-Aze-cha-Bta-Phe-NH_2 (52)

The linear peptide was prepared by linear peptide synthesis in accordance with AAV 1 and purified by HPLC. 10.5 mg of compound **52** were obtained as a white solid.

MS (ESI): m/z = 907.5 $[(M+H)^+]$.

Example 18: Synthesis von Ac-Phe-Orn-Pro-cha-Trp-NH-CH_2-CH_2-Ph (72)

200 mg Bromo-(4-methoxyphenyl) methyl polystyrene resin is incubated with 5 ml of a 50 % solution of phenylethylamine in THF (v/v) at RT for 18 h. Subsequently, the resin is washed (DMF; 3 x 5.0 ml, MeOH; 3 x 5.0 ml, DCM; 3 x 5.0 ml) and the peptide is synthesized in accordance with AAV 1. After purification by HPLC 4.1 mg of compound **72** were obtained as a white solid.

MS (ESI): m/z = 861.8 $[(M+H)^+]$.

Example 19: Synthesis ofAc-Phe-Orn-Aze-cha-Bta-Phe-NH-Me (95)

4.5 g 4-(4-formyl-3-methoxy-phenoxy)-butyl-acid-polystyrene resin was swollen for 15 min in THF. The resin was filtered off and reacted with a mixture of 3.04 g (10 eq.) methylamine-hydrochloride, 2.7 ml acetic acid, 2.7 ml trimethylorthoformiate and 90 ml THF. After one hour of stirring 2.83 g (10 eq.) sodium cyanoborhydride and 45 ml DMF were added. The mixture was stirred over night at room temperature, the resin was filtered off and washed with DMF (5x), MeOH (5x) und CH_2Cl_2 (5x). Subsequently, an amino acid coupling was performed using 968 mg (5 eq.) Fmoc-Phe-OH, 950 mg (5 eq.) HATU and 3.75 ml DIPEA in 10 ml DMF for two hours. The resin was filtered off and washed with DMF (5x), MeOH (5x) und CH_2Cl_2 (5x). 200 mg of the obtained resin was further used for linear peptide synthesis in accordance with AAV 1. Subsequent purification by HPLC yielded 10.0 mg of the desired product **95** as a white solid.

MS (ESI): m/z = 921.6 $[(M+H)^+]$.

Example 20: Synthesis of CH_3-SO_2-Phe-Orn-Aze-cha-Bta-Phe-NH_2 (96)

The peptide was prepared by linear peptide synthesis in accordance with AAV 1, whereby CH_3-SO_2-Cl was used instead of a N-terminal amino acid. Subsequent purification by HPLC yielded 5.5 mg of the desired product **96** as a white solid.

MS (ESI): m/z = 943.9 [$(M+H)^+$].

Example 21: Synthesis of H_2N-CO-Phe-Orn-Pro-cha-Bta-Phe-NH_2 (128)

The resin-bound peptide H-Phe-Orn-Pro-cha-Bta-Phe-Rink-amide resin was prepared in accordance with AAV 1. Subsequently, diphenylmethylisocyanate (5 eq.) and DIPEA (10 eq.) in DMF were added and agitated for two hours. After cleavage from the resin with a mixture of 95 % TFA, 2.5 % water and 2.5 % TIPS a purification by HPLC was performed. 0.92 mg of the compound was obtained as a white solid.

MS (ESI): m/z = 922.8 [$(M+H)^+$].

Example 22: Synthesis of (-CO-CH_2-NH-CO-)-Phe-Orn-Pro-cha-Bta-Phe-NH_2 (130)

The resin-bound peptide H-Gly-Phe-Orn-Pro-cha-Bta-Phe-Rink-amide resin was synthesized in accordance with AAV 1. Subsequently, the peptide was incubated for three hours with disuccinimidylcarbonate (3 eq.) and DIPEA (3 eq.) in DMF was added and agitated for 3 hours. Subsequently, additional 3 eq. DIPEA were added and the reaction was agitated for another five hours at room temperature. After cleavage from the resin with a mixture of 95 % TFA, 2.5 % water, and 2.5 % TIPS, purification was performed by HPLC. 3.8 mg of the compound were obtained as a white solid.

MS (ESI): m/z = 962.9 [$(M+H)^+$].

Example 23: Synthesis of (-CO-CH_2-CH_2-CO-)-Phe-Orn-Pro-cha-Bta-Phe-NH_2 (133)

The resin-bound peptide H-Phe-Orn-Pro-cha-Bta-Phe-Rink-amide resin was synthesized in accordance with AAV 1. Subsequently, succinic anhydride (5 eq.) and DIPEA (10 eq.) in DMF were added and the reaction agitated for two hours. The resin was filtered off and washed with DMF (5x), MeOH (5x), and CH_2Cl_2 (5x). Subsequently, the resin was incubated with HBTU (5 eq.) and DIPEA (10 eq.) in DMF for one day. The peptide was cleaved from the resin with a

mixture of 95 % TFA, 2.5 % water and 2.5 % TIPS and purified by HPLC, whereby 0.47 mg of the compound were obtained as a white solid.

MS (ESI): m/z = 961.9 $[(M+H)^+]$.

Example 24: Synthesis of FH_2C-CO-Phe-Orn-Pro-cha-Bta-Phe-NH_2 (142)

0.9 mg of the desired product **142** were obtained as a white solid after linear peptide synthesis in accordance with AAV 1, whereby fluoro-acetic acid was used rather than a N-terminal amino acid, and subsequent purification by HPLC.

MS (ESI): m/z = 939.8 $[(M+H)^+]$.

Example 25: Synthesis of Ac-Phe-Orn(Et_2)-Pro-cha-Trp-Phe-NH_2 (143)

10.0 mg of compound **51** were obtained after linear peptide synthesis in accordance with AAV 1 and subsequent purification by HPLC. 5.0 mg of this compound were dissolved in 5 ml THF and 1 ml acetaldehyde was added. The suspension was slowly stirred for 12 h at RT after addition of 100 mg (polystyrene methyl)trimethyl-ammoniumcyanoborhydride (3 mmol/g). Subsequently, the resin was filtered off and the mixture was evaporated to dryness. After purification by HPLC 1.2 mg of the desired compound **143** were obtained.

MS (ESI): m/z = 960.9 $[(M+H)^+]$.

Example 26: Synthesis of Ac-Phe-N(^{n}Bu)-CH_2-CO-Pro-cha-Trp-Phe-NH_2 (144)

The synthesis of the peptide H-Pro-cha-Trp-Phe-Rink-amide resin was performed in accordance with AAV 1. The free amino group was acylated with 4 ml of a 0.4 M solution of bromoactic acid anhydride in DCM (2x 15 min). The resin was washed with (DMF; 3 x 5.0 ml, MeOH; 3 x 5.0 ml, DCM; 3 x 5.0 ml) and then incubated for 2x 30 min in 4 ml of a 5 M solution of n-butylamine. After washing the resin with (DMF; 3 x 5.0 ml, MeOH; 3 x 5.0 ml, DCM; 3 x 5.0 ml) the remaining synthesis of the peptide was performed in accordance with AAV1.

Example 27: Synthesis of Ac-Phe-Arg(CH_2CH_2)-Pro-cha-Bta-Phe-NH_2 (150)

After linear peptide synthesis in accordance with AAV 1, 700 mg of Ac-Phe-Orn-Pro-cha-Bta-Phe-NH_2 (**62**) were obtained as crude product. To 15 mg of this crude product (0.016 mmol) 39.7 mg (10 eq.) 2-methylthio-2-imidazolin-hydroiodine and 55.4 µl (20 eq.) DIPEA in 1 ml MeCN were added and stirred at 40°C for one day. After removal of the solvent by using a rotary evaporator there was purification by HPLC and freeze drying after addition of 1 ml 0.1 N HCl and 0.5 ml MeCN, and 0.7 mg of compound **150** were obtained as white solid.

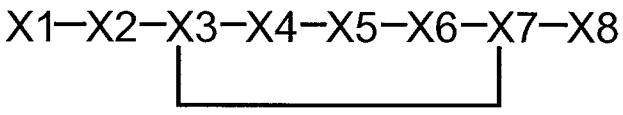
MS (ESI): m/z = 960.9 [$(M+H)^+$].

The features of the invention disclosed in the above description, the claims or the drawings can individually or in any combination be essential to the practice of the invention in its various embodiments.

C5 receptor analysis

Claims

1. A compound, preferably a C5a receptor antagonist, with the following structure:



(I)

, whereby

X1 is a radical having a mass of about 1-300 and whereby X1 is preferably chosen from the group including R5-, R5-CO-, R5-N(R6)-CO-, R5-O-CO-, R5-SO_2-, R5-N(R6)-SO_2-, R5-N(R6)-, R5-N(R6)-CS-, R5-N(R6)-C(NH)-, R5-CS-, R5-P(O)OH-, R5-B(OH)-, R5-CH=N-O-CH_2-CO-, in which R5 and R6 individually and independently are chosen from the group comprising H, F, hydroxy, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, arylalkyl, substituted arylalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, acyl, substituted acyl, alkoxy, alkoxyalkyl, substituted alkoxyalkyl, aryloxyalkyl and substituted aryloxyalkyl,

X2 is a radical that mimics the biologic binding characteristics of a phenylalanine unit,

X3 and X4 individually and independently are a spacer, whereby the spacer is preferably selected from the group comprising amino acids, amino acid analogs and amino acid derivates,

X5 is a radical that mimics the biologic binding characteristics of a cyclohexylalanine unit,

X6 is a radical that mimics the biologic binding characteristics of a tryptophane unit,

X7 is a radical that mimics the biologic binding characteristics of a norleucine or phenylalanine unit,

X8 is a radical, whereby the radical is optionally contained in structure I and if contained is selected from the group comprising H, NH2, OH, NH-OH, amino, substituted amino, alkoxy, substituted alkoxy, hydrazino, substituted hydrazino, aminoxy, substituted aminoxy, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocycyl, heteroaryl, substituted heteroaryl, arylalkyl, substituted arylalkyl, aryl, substituted aryl, amino acid, amino acid derivative and amino acid analogue.

a chemical bond is formed between X3 and X7, and

the lines – in formula (I) indicate chemical bonds, whereby the chemical bond is selected from the group comprising covalent bonds, ionic bonds and coordinative bonds, whereby preferably the bond is a chemical bond and more preferably the chemical bond is a bond selected from the group comprising amide bonds, disulfide bonds, ether bonds, thioether bonds, oxime bonds and aminotriazine bonds.

2. The compound according to claim 1, characterized in that X3 and X7 are individually an amino acid, amino acid analog or amino acid derivative, whereby the chemical bond between X3 and X7 is formed under participation of moieties of X3 and X7, and the moieties for X3 and X7 are individually and independently selected from the group comprising the C terminus, the N terminus and the respective side chain of the amino acid.

3. The compound according to claim 1 or 2, wherein

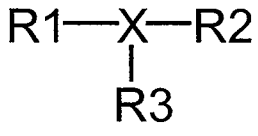
X1 is a radical with a mass of about 1-300, whereby the radical is preferably selected from the group comprising R5, R5-CO-, R5-N(R6)-CO-, R5-O-CO-, R5-SO_2-, R5-N(R6)-C(NH)-, whereby R5 and R6 are individually and independently selected from the group comprising H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl and substituted aryl;

X2 and X6 are individually and independently an aromatic amino acid, a derivative or an analogon thereof;

X5 and X7 are individually and independently a hydrophobic amino acid, a derivative or an analogon thereof.

4. The compound according to claim 3, characterised in that X1 is selected from the group comprising H, acetyl, butanoyl, benzoyl, fluoromethylcarbonyl, difluoromethylcarbonyl, phenyl, oxycarbonyl, methyl-oxycarbonyl, phenyl-aminocarbonyl, methyl-aminocarbonyl, phenyl-sulfonyl and methyl-sulfonyl.

5. Compound according to any of claims 1 to 4, whereby X2, X5 and X7 individually and independently have the following structure:



(III),

wherein

X is C(R4) or N,

R1 is optionally present and if present then R1 is a radical, that is selected from the group comprising >N-R1B, >C(R1B)(R1C) and >O, whereby R1B and R1C are individually and independently selected from the group comprising H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, arylalkyl, substituted arylalkyl, cycloalkylalkyl and substituted cycloalkylalkyl;

R2 is optionally present and if R2 is present then R2 is a radical that is selected from the group comprising C=O, C=S, SO_2, S=O, C=NH, C=N-CN, PO(OH), B(OH), CH_2, CH_2CO, CHF and CF_2;

R4 is a radical, whereby the radical is selected from the group comprising H, F, CH_3, CF_3, alkyl and substituted alkyl;

the binding of structure (III) to the moieties X1 and X3, X4 and X6, X5 and X7, and X6 and X8 is preferably carried out via R1 and R2;

for X2 and for X6 individually and independently R3 is a radical, in which the radical comprises an aromatic group and is selected from the group comprising aryl, substituted aryl, heteroaryl, substituted heteroaryl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, alkyloxy-alkyl, substituted alkyloxy-alkyl, alkyloxy-cycloalkyl, substituted alkyloxy-cycloalkyl, alkyloxy-heterocyclyl, substituted alkyloxy-heterocyclyl, alkyloxy-aryl, substituted alkyloxy-aryl, alkyloxy-heteroaryl, substituted alkyloxy-heteroaryl, alkylthio-alkyl, substituted alkylthio-alkyl, alkylthio-cycloalkyl and substituted alkylthio-cycloalkyl; and

for X5 and for X7 individually and independently R3 is a radical, whereby the radical comprises an aliphatic or aromatic group and preferably is seletected from the group comprising alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, cycloalkylalkyl, substituted cycloalkylalkyl, heterocyclylalkyl, substituted heterocyclylalkyl, alkyloxy-alkyl, substituted alkyloxy-alkyl, alkyloxy-cycloalkyl, substituted alkyloxy-cycloalkyl, alkyloxy-heterocyclyl, substituted alkyloxy-heterocyclyl, alkyloxy-aryl, substituted alkyloxy-aryl, alkyloxy-heteroaryl, substituted alkyloxy-heteroaryl, alkylthio-alkyl, substituted alkylthio-alkyl, alkylthio-cycloalkyl and substituted alkylthio-cycloalkyl.

6. The compound according to claim 5, characterized in that a ring is formed under participation of R3 and R4.

7. The compound according to claim 5 or 6, characterized in that for X2 and for X6 individually and independently R3 is selected from the group comprising phenyl, substituted phenyl, benzyl, substituted benzyl, 1,1-diphenylmethyl, substituted 1,1-diphenylmethyl, naphthylmethyl, substituted naphthylmethyl, thienylmethyl, substituted thienylmethyl, benzothienylmethyl, substituted benzothienylmethyl, imidazolylmethyl, substituted imidazolylmethyl, indolylmethyl and substituted indolylmethyl.

8 . The compound according to any of claims 5 to 7 characterized in that for X5 and for X7 individually and independently R3 is selected from the group comprising C3-C5-alkyl, substituted C3-C5-alkyl, C5-C7-cycloalkyl, substituted C5-C7-cycloalkyl, C5-C7-cycloalkylmethyl, substituted C5-C7-cycloalkylmethyl, cycloalkylethyl, substituted cycloalkylethyl, benzyl, substituted benzyl, phenylethyl, naphthylmethyl, thienylmethyl, propenyl, propinyl, methylthioethyl, imidazolylmethyl, substituted imidazolylmethyl, indolylmethyl and substituted indolylmethyl.

9. The compound according to any of claims 1 to 8, wherein

X2 is a derivative of an amino acid that is selected from the group comprising phenylalanine, 2-fluoro-phenylalanine, 3-fluoro-phenylalanine, 4-fluoro-phenylalanine, 2-chlorophenylalanine, 3-chlorophenylalanine, 4-chlorophenylalanine, 1-naphtylalanine, 2-thienylalanine, 3-thienylalanine, 3,3-diphenylalanine, tyrosine, tryptophane, histidine and each respective derivatives thereof;

or X2 and X1 taken together are $PhCH_2CH_2CO$- or $PhCH_2$-;

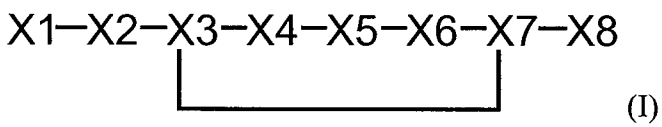
X6 is a derivative of an amino acid, that is selected from the group comprising tryptophane, phenylalanine, tyrosine, histidine, 1-naphtylalanine, benzothienylalanine, 2-aminoindan-2-carboxylic acid, 2-thienylalanine, 3-thienylalanine, 2-fluoro-phenylalanine, 3-fluoro-phenylalanine, 4-fluoro-phenylalanine, 2-chlorophenylalanine, 3-chlorophenylalanine, 4-chlorophenylalanine and respective derivatives thereof;

X5 is a derivative of an amino acid that is seletected from the group comprising D-cyclohexylalanine, D-cyclohexylglycine, D-homo-cyclohexylalanine, octahydroindol-2-carboxylic acid, 2-methyl-D-phenylalanine and respective derivatives thereof; and

X7 is a derivative of an amino acid that is seletected from the group comprising norvaline, norleucine, homo-leucine, leucine, isoleucine, Valine, cysteine, cysteine(Me), cysteine(Et), cysteine(Pr), methionine, allylglycine, propargylglycine, cyclohexylglycine, cyclohexylalanine, phenylalanine, tyrosine, tryptophane, histidine, 1-naphtylalanine, 2-thienylalanine, 3-thienylalanine and respective derivatives thereof.

10. The compound according to any of claims 1 to 9, wherein X1 and/or X4 comprise one or more groups that improve water solubility, whereby the water solubility improving group is seletected from the group comprising hydroxy, keto, carboxamido, ether, urea, carbamate, amino, substituted amino, Guanidino, pyridyl and carboxyl.

11. The compound, preferably a C5a receptor antagonist, having the following structure:



(I)

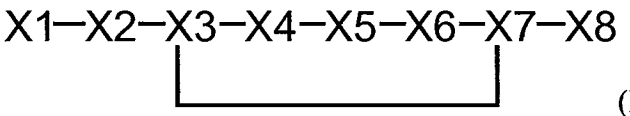
, whereby X1-X3 and X5-X8 are defined as in one of claims 1 to 10 and whereby

X4 is a cyclic or a non-cyclic amino acid, whereby the cyclic amino acid is seletected from the group comprising proline, pipecolinic acid, azetidine-2-carboxylic acid, tetrahydroisochinoline-3-carboxylic acid, tetrahydroisochinoline-1-carboxylic acid, octahydroindole-2-carboxylic acid, 1-aza-bicyclo-[3.3.0]-octane-2-carboxylic acid, 4-phenyl-pyrrolidine-2-carboxylic acid, cis-Hyp and trans-Hyp, and whereby the non-cyclic amino acid is selected from the group comprising Ser, Gln, Asn, Cys($O_2CH_2CH_2CONH_2$), Arg, Hyp($COCH_2OCH_2CH_2OCH_2CH_2OCH_3$), Hyp(CONH-$CH_2CH(OH)$-$CH_2OH$) and respective derivatives thereof and respective analogs thereof; and

the lines – in formula (I) indicate chemical bonds, whereby the chemical bond is selected from the group comprising covalent bonds, ionic bonds and coordinative bonds, whereby preferably the bond is a chemical bond and more preferably the chemical bond is a bond selected from the group comprising amide bonds, disulfide bonds, ether bonds, thioether bonds, oxime bonds and aminotriazine bonds.

12. The compound according to claim 11, characterized in that the amino acid represented by X4 is preferably selected from the group comprising proline, pipecolinic acid, azetidine-2-carboxylic acid, tetrahydroisochinoline-3-carboxylic acid, tetrahydroisochinoline-1-carboxylic acid, octahydroindole-2-carboxylic acid, 1-aza-bicyclo-[3.3.0]-octane-2-carboxylic acid, 4-phenyl-pyrrolidine-2-carboxylic acid, Hyp, Ser, Gln, Asn, Cys($O_2CH_2CH_2CONH_2$) and Arg.

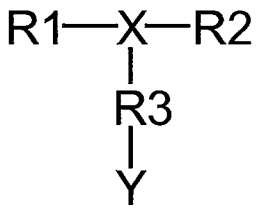
13. A compound, preferably a C5a receptor antagonist, of the structure



(I)

whereby X1-X2 and X4-X8 are defined as in any of claims 1 to 12 and whereby

X3 has the following structure



(IV),

wherein

X is C(R4) or N,

R1 is optionally present and if R1 is present then R1 is a radical which is selected from the group comprising >N-R1B, >C(R1B)(R1C) and >O, whereby R1B and R1C are individually and independently selected from the group comprising H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, arylakyl, substituted arylalkyl, cycloalkylalkyl and substituted cycloalkylalkyl;

R2 is optionally present and if R2 is present then R2 is a radical that is selected from the group comprising C=O, C=S, SO_2, PO(OH), B(OH), CH_2, CH_2CO, CHF and CF_2;

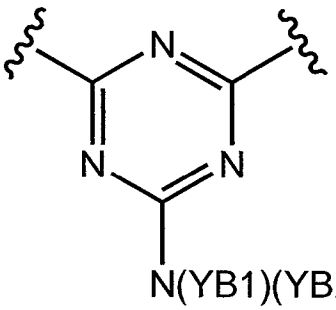
R4 is a radical, whereby the radical is selected from the group comprising H, F, CF_3, alkyl and substituted alkyl;

the binding of structure (IV) to the moieties X2 and X4 preferably takes place via R1 and R2;

R3 is a radical, whereby the radical is selected from the group comprising H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted

aryl, heteroaryl, substituted heteroaryl, cycloalkylalkyl, substituted cycloalkylalkyl, heterocyclylalkyl, substituted heterocyclylalkyl, arylalkyl, substituted arylalkyl, heteroarylalkyl and substituted heteroarylalkyl.

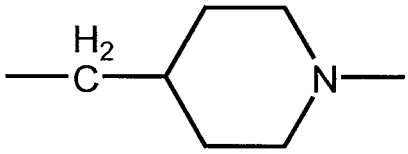
Y is optionally present and if Y is present then Y is a radical that is selected from the group comprising – N(YB)-, -O-, -S-, -S-S-, -CO-, -C=N-O-, -CO-N(YB)- and



, whereby YB, YB1 and YB2 are individually and independently selected from the group comprising H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, arylakyl, substituted arylalkyl, cycloalkylalkyl and substituted cycloalkylalkyl.

14. The compound according to claim 13, characterized in that

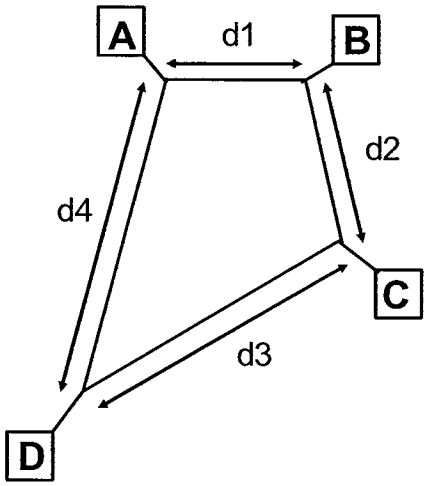
R3 is a radical selected from the group comprising methyl, ethyl, propyl, butyl, benzyl and



;

Y is optionally present and if Y is present then Y is a radical selected from the group comprising –N(YB)-, -O-, -S- and -S-S.

15. A compound, preferably a C5a receptor antagonist, whereby the compound has the following structure:



whereby d1, d2, d3 and d4 represent the distances of A, B, C and D in at least one energetically accessible conformer of the compound and have the following values:

d1 = 5.1 ± 1.0 Å

d2 = 11.5 ± 1.0 Å

d3 = 10.0 ± 1.5 Å

d4 = 6.9 ± 1.5 Å

A and C are individually and independently a hydrophobic radical, whereby the hydrophobic radical is selected from the group comprising alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

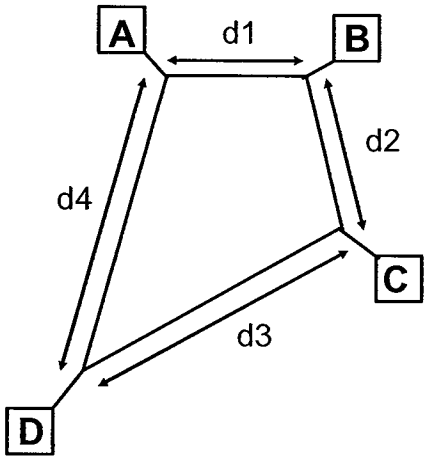
B and D are individually and independently an aromatic or a heteroaromatic radical, whereby preferably the aromatic radical is aryl, and preferably the heteroaromatic radical is heteroaryl.

16. The compound according to claim 15, whereby A and C are individually and independently selected from the group comprising C3-C6-alkyl, C5-C7-cycloalkyl, methylthioethyl, indolyl, phenyl, naphtyl, thienyl, propenyl, propinyl, hydroxyphenyl, indolyl and imidazolyl;

B is selected from the group comprising phenyl, naphthyl, thienyl, benzothienyl, hydroxyphenyl, indolyl, and imidazolyl; and

D is selected from the group comprising phenyl, naphthyl, thienyl, thiazolyl, furanyl, hydroxyphenyl, indolyl and imidazolyl.

17. A compound, preferably a C5a receptor antagonist, having the following structure:



, whereby

A, B, C and D represent the C-alpha atoms in amino acids, amino acid analogs or amino acid derivatives,

d1, d2, d3 and d4 represent the distances of A, B, C and D in at least one energetically accessible conformer of the compound and have the following values:

d1 = 3,9 ± 0,5 Å

d2 = 3,9 ± 0,5 Å

d3 = 9,0 ± 1,5 Å

d4 = 9,0 ± 1,5 Å;

whereby A and C, individually and independently have a hydrophobic amino acid side chain that comprises an alkyl-, cycloalkyl, heterocyclyl, aryl or heteroaryl,

B and D individually and independently have an aromatic or heteroaromatic amino acid side chain that comprises an aryl, or heteroaryl group.

18. The compound according to claim 17,

whereby A is seletected from the group comprising C3-C6-alkyl, methylthioethyl, propenyl, propinyl, R5, methyl-R5 and ethyl-R5, whereby R5 is a radical that is selected from the group comprising C5-C7-cycloalkyl, phenyl, substituted phenyl, hydroxyphenyl, indolyl, imidazolyl, naphtyl and thienyl;

whereby B is selected from the group comprising R5, methyl-R5 and ethyl-R5, whereby R5 is a selected from the group comprising phenyl, substituted phenyl, naphtyl, thienyl, benzothienyl, hydroxyphenyl, indolyl and imidazolyl;

whereby C is selected from the group comprising C3-C6-alkyl, R5, methyl-R5 and ethyl-R5, whereby R5 is a radical that is selected from the group comprising C5-C7-cycloalkyl, phenyl, 1-methyl-phenyl, 2-methyl-phenyl, 3-methyl-phenyl and S-tBu; and

whereby D is selected from the group comprising R5, methyl-R5 and ethyl-R5, whereby R5 is selected from the group comprising phenyl, naphthyl, thienyl, thiazolyl, furanyl, hydroxyphenyl, indolyl and imidazolyl.

19. A compound, preferably a C5a receptor antagonist, having the following structure:

$$X1–X2–X3–X4–X5–X6–X7–X8 \quad (II)$$

, whereby

X1 is a radical having a mass of about 1-300 and whereby X1 is preferably selected from the group comprising R5-, R5-CO-, R5-N(R6)-CO-, R5-O-CO-, R5-SO_2-, R5-N(R6)-SO_2-, R5-N(R6)-, R5-N(R6)-CS-, R5-N(R6)-C(NH)-, R5-CS-, R5-P(O)OH-, R5-B(OH)-, R5-CH=N-O-CH_2-CO-, whereby R5 and R6 are individually and independently selected from the group comprising H, F, hydroxy, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, arylalkyl, substituted arylalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, acyl, substituted acyl, alkoxy, alkoxyalkyl, substituted alkoxyalkyl, aryloxyalkyl and substituted aryloxyalkyl,

X2 is a radical that mimics the biological binding characteristics of a phenylalanine unit,

X3 and X4 are individually and independently a spacer, whereby the spacer is preferably selected from the group comprising amino acids, amino acid analogs and amino acid derivates,

X5 is a radical that mimics the biological binding characteristics of a cyclohexylalanine unit,

X6 is a radical that mimics the biological binding characteristics of a tryptophane unit,

X7 is a radical that mimics the biological binding characteristics of a norleucine or phenylalanine unit,

X8 is a radical, whereby the radical is optionally present in structure I, and if it is present, it is selected from the group comprising H, NH_2, OH, NH-OH, amino, substituted amino, alkoxy, substituted alkoxy, hydrazino, substituted hydrazino, aminooxy, substituted aminooxy, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, heteroaryl, substituted heteroaryl, arylalkyl, substituted arylalkyl, aryl, substituted aryl, amino acid, amino acid derivative and amino acid analogon;

the connecting lines – in formula (II) represent chemical bonds, whereby the chemical bond is selected from the group comprising covalent bonds, ionic bonds and coordinative bonds, whereby preferably the bond is a chemical bond and more preferably the chemical bond is a bond selected from the group comprising amide bonds, disulfide bonds, ether bonds, thioether bonds, oxime bonds and aminotriazine bonds.

20. The compound according to claim 19, whereby

X1 is a radical having a mass of about 1-300, whereby the radical is preferably selected from the group comprising R5, R5-CO-, R5-N(R6)-CO-, R5-O-CO-, R5-SO_2-, R5-N(R6)-C(NH)-, whereby preferably R5 and R6 are individually and independently selected from the group comprising H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl and substituted aryl;

X2 and X6 are individually and independently an aromatic amino acid, a derivative or an analogon thereof,

X5 and X7 are individually and independently a hydrophobic amino acid, a derivative or an analogon thereof.

21. Compound according to claim 20, characterised in that X is selected from the group comprising H, acetyl, propanyl, butanoyl, benzoyl, fluoromethylcarbonyl, difluoromethylcarbonyl, phenyl, oxycarbonyl, methyloxycarbonyl, phenylaminocarbonyl, methylaminocarbonyl, phenylsulfonyl and methylsulfonyl.

22. The compound according to any of claims 19 to 21, whereby X2, X5, X6 and X7 have individually and independently the following structure:

(III),

whereby

X is C(R4) or N,

R1 is a radical that is selected from the group comprising >N-R1B, >C(R1B)(R1C) and >O, whereby R1B and R1C are individually and independently selected from the group comprising H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, arylalkyl, substituted arylalkyl, cycloalkylalkyl and substituted cycloalkylalkyl;

R2 is optionally present and if R2 is present, it is a radical selected from the group comprising C=O, C=S, SO_2, S=O, C=NH, C=N-CN, PO(OH), B(OH), CH_2, CH_2CO, CHF and CF_2;

R4 is a radical, whereby the radical is selected from the group comprising H, F, CH_3, CF_3, alkyl and substituted alkyl;

and the binding of structure (III) to the moieties X1 and X3, X4 and X6, X5 and X7, and X6 and X8 preferably takes place via R1 and R2;

for X2 and for X6 individually and independently R3 is a radical, whereby the radical comprises an aromatic group and is selected from the group comprising aryl, substituted aryl, heteroaryl, substituted heteroaryl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, alkyloxy-alkyl, substituted alkyloxy-alkyl, alkyloxy-cycloalkyl, substituted alkyloxy-cycloalkyl, alkyloxy-heterocyclyl, substituted alkyloxy-heterocyclyl, alkyloxy-aryl, substituted alkyloxy-aryl, alkyloxy-heteroaryl, substituted alkyloxy-heteroaryl, alkylthio-alkyl, substituted alkylthio-alkyl, alkylthio-cycloalkyl and substituted alkylthio-cycloalkyl; and

for X5 and for X7 individually and independently R3 is a radical, whereby the radical comprises an aliphatic or aromatic group and preferably is selected from the group comprising alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, cycloalkylalkyl, substituted cycloalkylalkyl, heterocyclylalkyl, substituted heterocyclylalkyl, alkyloxy-alkyl, substituted alkyloxy-alkyl, alkyloxy-cycloalkyl, substituted alkyloxy-cycloalkyl, alkyloxy-heterocyclyl, substituted alkyloxy-heterocyclyl, alkyloxy-aryl, substituted alkyloxy-aryl, alkyloxy-heteroaryl, substituted

alkyloxy-heteroaryl, alkylthio-alkyl, substituted alkylthio-alkyl, alkylthio-cycloalkyl and substituted alkylthio-cycloalkyl.

23. The compound according to claim 22, characterized in that a ring is formed using R3 and R4.

24. The compound according to claim 22 or 23, characterized in that for X2 and for X6 individually and independently R3 is selected from the group comprising phenyl, substituted phenyl, benzyl, substituted benzyl, 1,1-diphenylmethyl, substituted 1,1-diphenylmethyl, naphthylmethyl, substituted naphthylmethyl, thienylmethyl, substituted thienylmethyl, benzothienylmethyl, substituted benzothienylmethyl, imidazolylmethyl, substituted imidazolylmethyl, indolylmethyl and substituted indolylmethyl.

25. The compound according to any of claims 19 to 24, characterized in that for X5 and for X7 individually and independently R3 is selected from the group comprising C3-C5-alkyl, substituted C3-C5-alkyl, C5-C7-cycloalkyl, substituted C5-C7-cycloalkyl, C5-C7-cycloalkylmethyl, substituted C5-C7-cycloalkylmethyl, cycloalkylethyl, substituted cycloalkylethyl, benzyl, substituted benzyl, phenylethyl, naphthylmethyl, thienylmethyl, propenyl, propinyl, methylthioethyl, imidazolylmethyl, substituted imidazolylmethyl, indolylmethyl and substituted indolylmethyl.

26. The compound according to any of claims 19 to 25, whereby X2 is an amino acid dervative of an amino acid selected from the group comprising phenylalanine, 2-fluoro-phenylalanine, 3-fluoro-phenylalanine, 4-fluoro-phenylalanine, 2-chloro-phenylalanine, 3-chloro-phenylalanine, 4-chlorophenylalanine, 1-naphthylalanine, 2-thienylalanine, 3-thienylalanine, 3, 3-diphenylalanine, tyrosine, tryptophane, histidine and respective derivatives thereof;

or X2 and X1, taken together, are $PhCH_2CH_2CO$- or $PhCH_2$; X6 is an amino acid derivative of an amino acid selected from the group comprising tryptophane, phenylalanine, tyrosine, histidine, 1-naphthylalanine, benyothienylalanine, 2-aminoindane-2-carboxylic acid, 2-thienylalanine, 3-thienylalanine, 2-fluoro-phenylalanine, 3-fluoro-phenylalanine, 4-fluoro-

phenylalanine, 2-chloro-phenylalanines, 3-chloro-phenylalalanines, 4-chloro-phenylalanines and the respective derivatives thereof;

X5 is an amino acid derivative of an amino acid selected from the group comprising D-cyclohexylalanine, D-cyclohexylglycine, D-homo-cyclohexylalanine, octahydroindole-2-carboxylic acid, 2-methyl-D-phenylalanine and the respective derivatives thereof;

and

X7 is an amino acid dervative of an amino aicd selected from the group comrising norvaline, norleucine, homo-leucine, leucine, isoleucine, valine, cysteine, cystein (Me), cystein (Et), cystein (Pr), methionine, allylglycine, propargylglycine, cyclohexylglycine, cyclohexylalanine, phenylalanine, tyrosine, tryptophane, histidine, 1-naphthylalanine, 2-thienylalanine, 3-thienylalanine and the respective derivatives thereof.

27. The compound according to any of claims 19 to 26, whereby X1 and/or X4 comprise one or more groups that improve water solubility, whereby the water solubility improving group is selected from the group comprising hydroxy, keto, carboxamido, ether, urea, carbamate, amino, substituted amino, guanidino, pyridyl and carboxyl.

28. A compound, preferably a C5a receptor antagonist, having the following structure:

X1–X2–X3–X4–X5–X6–X7–X8 (II)

, whereby X1-X3 and X5-X8 are defined as in any of claims 17 to 26 and whereby

X4 is a cyclic or a non-cyclic amino acid, whereby the cyclic amino acid is selected from the group comprising proline, pipecolic acid, azetidine-2-carbonic acid, tetrahydroisoquinoline-3-carboxylic acid, tetrahydroisoquinoline-1-carboxylic acid, octahydroindole-2-carboxylic acid, 1-aza-bicyclo-[3.3.0]-octane-2-carboxylic acid, 4-phenyl-pyrrolidine-2-carboxylic acid, cis-Hyp and trans-Hyp, and the non-cyclic amino acid is selected from the group comprising Ser, Gln,

Asn, Cys($O_2CH_2CH_2CONH_2$), Arg, Hyp($COCH_2OCH_2CH_2OCH_2CH_2OCH_3$), Hyp(CONH-$CH_2CH(OH)$-$CH_2OH$) and respective derivatives thereof and respective analogs thereof; and

the connecting lines – in formula (I) represent chemical bonds, whereby preferably the chemical bond is selected from the group comprising covalent bonds, ionic bonds and coordinative bonds, whereby preferably the bond is a chemical bond and more preferably the chemical bond is a bond selected from the group comprising amide bonds, disulfide bonds, ether bonds, thioether bonds, oxime bonds and aminotriazine bonds.

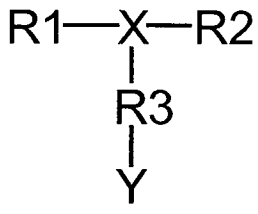
29. The compound according to claim 28, characterized in that the amino acids are preferably selected from the group comprising proline, Pipecolic acid, azetidine-2-carboxylic acid, tetrahydroisoquinoline-3-carboxylic acid, tetrahydroisoquinoline-1-carboxylic acid, octahydroindole-2-carboxylic acid, 1-aza-bicyclo-[3.3.0]-octane-2-carboxylic acid, 4-phenyl-pyrrolidine-2-carboxylic acid, Hyp, Ser, Gln, Asn, Cys($O_2CH_2CH_2CONH_2$) and Arg.

30. A compound, preferably a C5a receptor antagonist, having the following structure:

X1--X2--X3--X4--X5--X6--X7--X8 (II)

, whereby X1-X2 and X4-X8 are defined as in any of claims 19 to 29 and whereby

X3 has the following structure:



(IV),

whereby

X is C(R4) or N,

R1 is optionally present and if R1 is present it is a radical selected from the group comprising >N-R1B, >C(R1B)(R1C) and >O, whereby R1B and R1C are individually and independently

selected from the group comprising H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, arylakyl, substituted arylalkyl, cycloalkylalkyl and substituted cycloalkylalkyl;

R2 is optionally present and if R2 is present it is a radical selected from the group comprising C=O, C=S, SO_2, PO(OH), B(OH), CH_2, CH_2CO, CHF and CF_2;

R4 is a radical, whereby the radical is selected from the group comprising H, F, CH_3, CF_3, alkyl and substituted alkyl;

the binding of structure (IV) to the moieties X2 and X4 preferably takes place via R1 and R2;

R3 is a radical selected from the group comprising H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkylalkyl, substituted cycloalkylalkyl, heterocyclyl, substituted heterocyclyl, heterocyclylalkyl, substituted heterocyclylalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, acyl, substituted acyl, alkoxyalkyl, substituted alkoxyalkyl, aryloxyalkyl, substituted aryloxyalkyl, sulfhydrylalkyl, substituted sulfhydrylalkyl, hydroxyalkyl, substituted hydroxyalkyl, carboxyalkyl, substituted carboxyalkyl, carboxamidoalkyl, substituted carboxamidoalkyl, carboxyhydrazinoalkyl, ureidoalkyl aminoalkyl, substituted aminoalkyl, guanidinoalkyl and substituted guanidinoalkyl;

Y is optionally present and if present is a radical that is selected from the group comprising H, -N(YB1)-CO-YB2, -N(YB1)-CO-N(YB2)(YB3), -N(YB1)-C(N-YB2)-N(YB3)(YB4), -N(YB1)(YB2), -N(YB1)-SO_2-YB2, O-YB1, S-YB1, -CO-YB1, -CO-N(YB1)(YB2) and -C=N-O-YB1, whereby YB1, YB2, YB3 and YB4 are individually and independently selected from the group comprising H, CN, NO_2, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, arylakyl, substituted arylalkyl, cycloalkylalkyl and substituted cycloalkylalkyl.

31 . The compound according to claim 30, characterized in that

R3 is a radical having the structure

$-(CH_2)_m-Y$ (VII)

or

$-(CH_2)_m-C_6H_4-Y$ (VIII) ist

, whereby

m is 1, 2, 3 or 4;

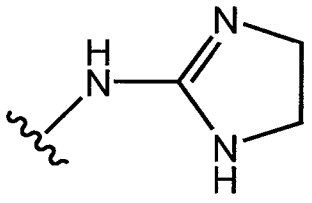
Y is N(R3b)(R3c) or -N(YB1)-C(N-YB2)-N(YB3)(YB4), whereby R3b, R3c, YB1, YB2, YB3 and YB4 are individually and independently selected from the group comprising H, CN and alkyl.

32. The compound according to claim 30 or 31, characterized in that a ring is formed between two group, whereby the groups are individually and independently selected from the group comprising YB1, YB2, YB3 and YB4.

33. The compound according to claim 32, characterized in that the ring is formed by YB2 and YB3.

34. The compound according to any of claims 30 to 33, characterized in that Y is

$-NH_2$



or (VII).

35. The compound according to any of the preceding claims, whereby the compound is one of the following compounds:

No.	Compound
1	Ac-Phe-[Orn-Pro-cha-Trp-Phe]
2	Ac-Phe-[Orn-Hyp-cha-Trp-Phe]

3	$HOCH_2(CHOH)_4$-C=N-O-CH_2-CO-Phe-[Orn-Pro-cha-Trp-Nle]
4	X-Phe-[Orn-Pro-cha-Trp-Nle]; X = 2-acetamido-1-methyl-glucuronyl
5	Ac-Phe-[Orn-Hyp($COCH_2OCH_2CH_2OCH_2CH_2OCH_3$)-cha-Trp-Nle]
6	Ac-Phe-[Orn-Hyp(CONH-$CH_2CH(OH)$-CH_2OH)-cha-Trp-Nle]
20	Ac-Phe-[Orn-Pro-cha-Trp-Ecr]
28	Ac-Phe-[Orn-Pro-cha-Trp-Nle]
29	Ac-Phe-[Orn-Pro-cha-Trp-Met]
31	Ac-Phe-[Orn-Pro-cha-Trp-Nva]
32	Ac-Phe-[Orn-Pro-cha-Trp-Hle]
33	Ac-Phe-[Orn-Pro-cha-Trp-Eaf]
34	Ac-Phe-[Orn-Pro-cha-Trp-Ebd]
35	Ac-Phe-[Orn-Pro-cha-Trp-Eag]
36	Ac-Phe-[Orn-Pro-cha-Trp-Pmf]
37	Ac-Phe-[Orn-Pro-cha-Trp-2Ni]
38	Ac-Phe-[Orn-Pro-cha-Trp-Thi]
41	Ph-CH_2-CH_2-CO-[Orn-Pro-cha-Trp-Nle]
42	H-Phe-[Orn-Pro-cha-Trp-Nle]
43	Ac-Lys-Phe-[Orn-Pro-cha-Trp-Nle]
44	H-Phe-[Orn-Ser-cha-Trp-Nle]
51	Ac-Phe-Orn-Pro-cha-Trp-Phe-NH_2
52	Ac-Phe-Orn-Aze-cha-Bta-Phe-NH_2
53	Ac-Phe-Orn-Pro-cha-Bta-2Ni-NH_2
54	Ac-Phe-Orn-Pro-cha-Bta-Cha-NH_2
55	Ac-Phe-Orn-Pip-cha-Trp-Phe-NH_2
56	Ph-CH_2-[Orn-Pro-cha-Trp-Nle]
57	Ph-CH_2-[Orn-Pro-cha-Trp-Phe]
58	Ac-Phe-[Orn-Pro-cha-Trp-1Ni]
59	Ph-CH(OH)-CH_2-CO-[Orn-Pro-cha-Trp-Nle]
61	Ac-Phe-Orn-Pro-cha-Trp-Phe-NH_2

62	Ac-Phe-Orn-Pro-cha-Bta-Phe-NH_2
64	Ac-Phe-Orn-Pro-cha-Trp-2Ni-NH_2
65	Ac-Phe-Orn-Pro-cha-Trp-Cha-NH_2
66	Ac-Thi-Orn-Aze-cha-Bta-Phe-NH_2
67	Ac-Thi-Orn-Pip-cha-Bta-Phe-NH_2
68	Ac-Phe-Orn-Pro-cha-Trp-Eap-NH_2
69	Me_2-Phe-Orn-Pro-cha-Trp-Phe-NH_2
70	Ph_2-CH-CH_2-CO-Orn-Pro-cha-Trp-Phe-NH_2
71	Ac-Ebw-Orn-Pro-cha-Trp-Phe-NH_2
72	Ac-Phe-Orn-Pro-cha-Trp-NH-CH_2-CH_2-Ph
73	Ac-Phe-Orn-Aze-cha-Bta-NH-CH_2-CH_2-Ph
74	H-Phe-Orn-Pro-cha-Trp-Phe-NH_2
75	H-Me-Phe-Orn-Pro-cha-Trp-Phe-NH_2
76	Bu-NH-CO-Phe-Orn-Pro-cha-Trp-Phe-NH_2
77	Ac-Thi-Orn-Pro-cha-Trp-Phe-NH_2
78	Ac-Ebw-Orn-Pro-cha-Trp-Phe-NH_2
79	Ac-Phe-Orn-Ala-cha-Trp-Phe-NH_2
80	Ac-Phe-Orn-Pro-cha-Trp-Thi-NH_2
81	Ac-Phe-Orn-Aze-cha-Pcf-Phe-NH_2
82	Ac-Phe-Orn(Ac)-Pro-cha-Trp-Phe-NH_2
83	Ac-Phe-Orn-Aze-cha-Trp-Phe-NH_2
84	Ac-Phe-Trp-Pro-cha-Trp-Phe-NH_2
85	Ph-NH-CO-Phe-Orn-Pro-cha-Trp-Phe-NH_2
86	Bu-O-CO-Phe-Orn-Pro-cha-Trp-Phe-NH_2
87	Ac-Phe-Lys-Pro-cha-Trp-Phe-NH_2
88	Ac-Phe-Arg-Pro-cha-Trp-Phe-NH_2
89	Ac-Phe-Gln-Pro-cha-Trp-Phe-NH_2
92	Ac-Phe-Orn-Pip-cha-Trp-Phe-NH_2
93	Ac-Phe-Orn-Hyp-cha-Trp-Phe-NH_2
94	Ac-Phe-Orn-Pro-cha-Trp-1Ni-NH_2
95	Ac-Phe-Orn-Aze-cha-Bta-Phe-NH-Me
96	CH_3-SO_2-Phe-Orn-Aze-cha-Bta-Phe-NH_2
99	Ac-Phe-Orn-Aze-cha-Pff-Phe-NH_2

100	Ac-Phe-Orn-Aze-cha-Mcf-Phe-NH_2
101	Ac-Phe-Orn(Ac)-Aze-cha-Bta-Phe-NH_2
102	Ac-Ebw-Orn-Pro-cha-Trp-Phe-NH_2
103	Ac-Phe-Trp-Pro-cha-Trp-Phe-NH_2
104	Ac-Phe-Arg-Pro-cha-Trp-Phe-NH_2
105	Ac-Phe-Orn-Pip-cha-Trp-Phe-NH_2
106	3PP-Orn-Aze-cha-Bta-Phe-NH_2
107	Ac-Phe-Orn-Tic-cha-Trp-Phe-NH_2
108	Ac-Phe-Orn-Ser-cha-Trp-Phe-NH_2
109	Ac-Phe-Orn-Pro-chg-Trp-Phe-NH_2
110	Ac-Phe-Orn-Pro-hch-Trp-Phe-NH_2
111	Ac-Phe-Orn-Pro-cha-Trp-Phg-NH_2
112	Ac-Phe-Bta-Aze-cha-Bta-Phe-NH_2
113	Ac-Phe-Trp-Pro-cha-Bta-Phe-NH_2
115	Ac-Phe-Orn-Pip-cha-Trp-Phe-OH
116	Ac-Phe-Orn-Tic-cha-Trp-Phe-OH
117	Ac-Phe-Orn-Ser-cha-Trp-Phe-OH
118	Ac-Phe-Orn-Pro-chg-Trp-Phe-OH
119	Ac-Phe-Eec-Pro-cha-Bta-Phe-NH_2
120	Ac-Phe-Nle-Pro-cha-Bta-Phe-NH_2
121	Ac-Phe-Har-Pro-cha-Bta-Phe-NH_2
122	Ac-Phe-Arg-Pro-cha-Bta-Phe-NH_2
123	Ac-Phe-Cys(Acm)-Pro-cha-Bta-Phe-NH_2
124	Ac-Phe-Mpa-Pro-cha-Bta-Phe-NH_2
125	Ac-Eby-Orn-Pro-cha-Bta-Phe-NH_2
126	Ac-Phg-Orn-Pro-cha-Bta-Phe-NH_2
127	Ac-Phe-Paf-Pro-cha-Bta-Phe-NH_2
128	H_2N-CO-Phe-Orn-Pro-cha-Bta-Phe-NH_2
129	Me-O-CO-Phe-Orn-Pro-cha-Bta-Phe-NH_2
130	(-CO-CH_2-NH-CO-)-Phe-Orn-Pro-cha-Bta-Phe-NH_2
132	Ac-Phe-Orn-Pro-hch-Trp-Phe-OH
133	(-CO-CH_2-CH_2-CO-)-Phe-Orn-Pro-cha-Bta-Phe-NH_2
134	^{t}Bu-CO-Phe-Orn-Pro-cha-Bta-Phe-NH_2

135	Ac-Lys-Phe-Orn-Aze-cha-Bta-Phe-NH_2
136	Ac-Gly-Phe-Orn-Aze-cha-Bta-Phe-NH_2
137	Ac-Arg-Phe-Orn-Aze-cha-Bta-Phe-NH_2
138	Ac-His-Phe-Orn-Aze-cha-Bta-Phe-NH_2
139	Ac-Ser-Phe-Orn-Aze-cha-Bta-Phe-NH_2
140	Ac-Guf-Phe-Orn-Aze-cha-Bta-Phe-NH_2
141	Ac-Dab-Phe-Orn-Aze-cha-Bta-Phe-NH_2
142	FH_2C-CO-Phe-Orn-Pro-cha-Bta-Phe-NH_2
143	Ac-Phe-Orn(Et_2)-Pro-cha-Trp-Phe-NH_2
144	Ac-Phe-[Orn-Hyp-cha-Trp-Nle]
145	3PP-[Orn-Hyp-cha-Trp-Nle]
146	Ac-Phe-[Orn-Pro-cha-Trp-Tyr]
147	Ac-Phe-[Orn-Pro-omf-Trp-Nle]
149	Ac-Phe-Orn-Pro-hle-Bta-Phe-NH_2
150	Ac-Phe-Arg(CH_2-CH_2)-Pro-cha-Bta-Phe-NH_2

36. A pharmaceutical composition comprising at least one compound according to any of the preceding claims and additionally a pharmaceutically acceptable carrier.

37. Use of at least one of the compounds according to one of the preceding claims for the manufacture of a medicament.

38. Use according claim 46, characterized in that the medicament is used for the prevention and/or treatment of a condition associated with complement activation and/or where the inhibition of the complement system leads to a relief of the symptoms.

39. Use according to claim 37, characterized in that the condition and/or the symptoms to be treated are selected from the group comprising rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, psoriasis, septic shock, asthma, vasculitis, dermatomyositis, inflammatory bowel disease (IBD), pemphigus, myasthenia gravis, acute respiratory insufficiency, stroke, myocardial infarction, reperfusion injury, burn, and acute injuries of the central nervous system.

40. Use of at least one compound according to any of the preceding claims for the prevention and/or support of surgery.

41. Use according to claims 37 to 38, characterized in that the medicament is used for the prevention and/or the support of surgery.

42. Use according claim 37, characterized in that the medicament is used for the prevention and/or support and/or post-operative treatment of a surgery, whereby the surgery is selected from the group comprising CABG; PACT; PTA, MidCAB, OPCAB, thrombolysis, and vascular occlusion (clamping).

43. Use according to claim 37, whereby the medicament is used for thrombolytic treatment.

44. Use according to claim 37, characterized in that the medicament is used in the settings of dialysis therapy, optionally before, during, and/or after such therapy.

Summary

The present invention is related to a compound, preferably a C5a receptor antagonist, having the following structure:

X1–X2–X3–X4–X5–X6–X7–X8 (I)

, whereby

X1 is a radical with a mass of about 1-300, whereby X1 is preferably selected from the group comprising R5-, R5-CO-, R5-N(R6)-CO-, R5-O-CO-, R5-SO_2-, R5-N(R6)-SO_2-, R5-N(R6)-, R5-N(R6)-CS-, R5-N(R6)-C(NH)-, R5-CS-, R5-P(O)OH-, R5-B(OH)-, R5-CH=N-O-CH_2-CO-, whereby R5 and R6 are individually and independently selected from the group comprising H, F, hydroxy, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, arylalkyl, substituted arylalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, acyl, substituted acyl, alkoxy, alkoxyalkyl, substituted alkoxyalkyl, aryloxyalkyl and substituted aryloxyalkyl,

X2 is a radical that mimics the biological binding characteristics of a phenylalanine unit,

X3 and X4 are individually and independently a spacer, whereby the spacer is preferably selected from the group comprising amino acids, amino acid analogs and amino acid derivates,

X5 is a radical that mimics the biological binding characteristics of a cyclohexylalanine unit,

X6 is a radical that mimics the biological binding characteristics of a tryptophane unit,

X7 is a radical that mimics the biological binding characteristics of a norleucine or phenylalanine unit,

X8 is a radical, whereby the radical is optionally contained in structure I and, if contained, selected from the group comprising H, NH_2, OH, NH-OH, amino, substituted amino, alkoxy,

substituted alkoxy, hydrazino, substituted hydrozino, aminooxy, substituted aminooxy, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, heteroaryl, substituted heteroaryl, arylalkyl, substituted arylalkyl, aryl, substituted aryl, amino acid, amino acid derivative and amino acid analogue,

a chemical bond is formed between X3 and X7, and

the connecting lines – in formula (I) represent chemical bonds, whereby the chemical bond is selected from the group comprising covalent bonds, ionic bonds and coordinative bonds, whereby preferably the bond is a chemical bond and more preferably the chemical bond is a bond selected from the group comprising amide bonds, disulfide bonds, ether bonds, thioether bonds, oxime bonds and aminotriazine bonds.